

Francisco Bandeira · Hossein Gharib  
Airton Golbert · Luiz Griz · Manuel Faria *Editors*

# Endocrinology and Diabetes

A Problem-Oriented Approach

 Springer

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Editors

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## Preface

Endocrinology is a fast-growing field, and endocrine literature is huge. With an ever-increasing body of data that includes original studies, therapeutic trials, new tests, reports on new treatments, and guidelines for management, most clinicians are overwhelmed, if not confused, with new information. Given the extent and pace of new developments in endocrinology, we felt that there is a need and a place for a concise, clinically oriented, up-to-date endocrine text. We hope that the problem-oriented format will provide the reader a unique and convenient approach to endocrine problems, from presentation, to diagnostic tests, to specific treatment, and to appropriate follow-up. Our contributors have provided the readers with a practical approach to most common endocrine disorders.

We express our sincere and enduring gratitude to our international colleagues for sharing their expertise and writing chapters for the book. It is our hope that information and recommendations in this text will help our friends and colleagues who provide endocrine care worldwide.

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## Introduction

As the genetic basis of an increasing number of endocrine disorders is appreciated, it has become essential for the clinical endocrinologist to have a good understanding of the genetics of endocrine disease. The term “genetic disease” can be confusing and needs clarification. Traditionally, this term has been used in the context of chromosomal disorders such as Klinefelter syndrome (47,XXY), or rare Mendelian disorders (also known as monogenic disorders) such as multiple endocrine neoplasia type 1 or type 2 (MEN1 or MEN2). Since we now realize that common disorders such as type 2 diabetes mellitus (T2DM) and obesity have strong genetic components [1–4], the term “genetic disease” could be applied to such disorders as well. It is probably better though to maintain the distinction between monogenic disorders such as MEN1, and polygenic or multifactorial disorders such as T2DM (Fig. 1.1). One must appreciate the fact though that a mutation in *MEN1* is not presumed to act in isolation, and that the rest of the person’s genetic background will usually influence the phenotypic presentation of the disease. Likewise, the many different genes associated with a multifactorial disorder such as T2DM will each individually

play a small role, but environmental influences such as diet and exercise together with this genetic predisposition will determine the risk of this complex disorder. We are just beginning to understand these gene–gene and gene–environment interactions and our ability to truly practice individualized medicine depends on a better understanding of these complex interactions.

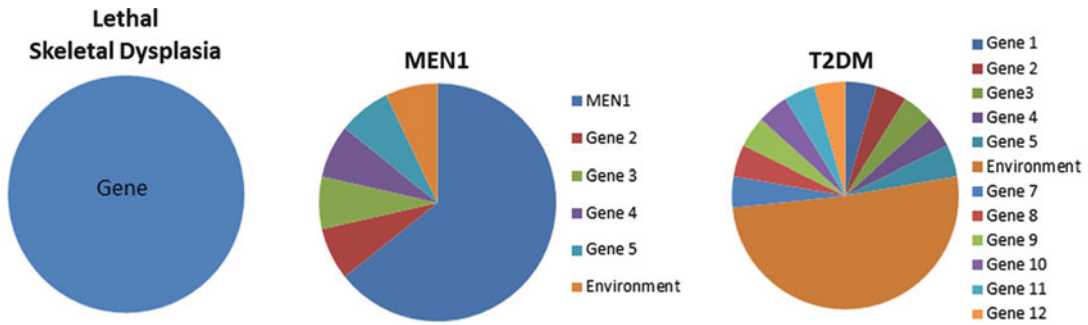
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## The Role of Genetic Testing in the Clinic

The busy practitioner is challenged on a daily basis to recognize clinical scenarios that may be indicative of a genetic condition. This requires the recognition of clinical patterns, as well as taking a good family history. There are a number of reasons why genetic testing is important in the clinical setting (Table 1.1). An accurate diagnosis not only directs current management but also allows for a personalized road map for future surveillance for patients and presymptomatic family members. With the advent of prenatal and preimplantation diagnosis of genetic disorders, couples at risk for having children with heritable endocrine disorders may want to use genetic information to make reproductive decisions, and need appropriate counseling about the options available to them. Finally, with the flood of data coming in from genome-wide association studies (GWAS), and now with whole-exome and whole-genome sequencing, endocrinologists need to be ready for the demands of practicing individualized medicine for all of their patients.

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**Fig. 1.1** The cost of DNA sequencing

**Table 1.1** Clinical utility of genetic testing

- Accurate diagnosis and prognosis
- Tailor management and surveillance for affected individuals
- Identify presymptomatic individuals in affected families
- Offer reproductive options to couples at risk

To understand the significance of genetic test results, one has to first understand the importance of genetic variation in individuals. The sequence of nuclear DNA is nearly 99.9 % identical between any two humans [5]. Some DNA sequence differences have little or no effect on phenotype, whereas others are directly responsible for causing disease. Between these two extremes is the variation responsible for genetically determined phenotypic variability amongst individuals. Genetic disease is only the most obvious and extreme manifestation of genetic differences.

## Gene Structure and Molecular Testing

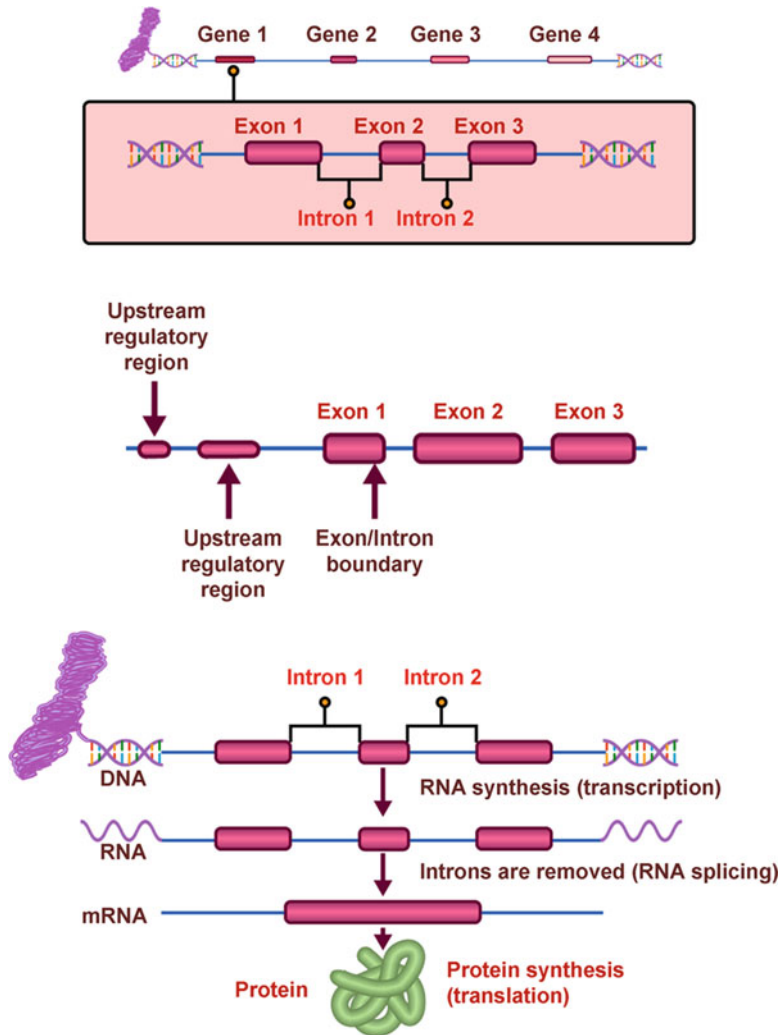
There are approximately 25,000 genes in each of our cells. Even though the human genome has been sequenced, we still do not understand the functional significance of all of our genes. The coding regions of a gene (exons) are interspersed between large noncoding regions called introns (Fig. 1.2). Through the process of transcription and translation, the introns are spliced out to form messenger RNA (mRNA),

which directs the formation of a specific protein. This process is influenced by noncoding regions such as promoters and enhancers, as well as regulatory regions upstream or downstream of the gene.

A mutation is simply a change in the nucleotide sequence of a gene. Most pathogenic mutations occur within exons, but they may also occur at the junction of introns and exons and thus affect splicing or, more rarely, occur in regulatory areas of the gene.

There are many different types of mutations, as illustrated in Fig. 1.3.

There are many different types of genetic tests (Table 1.2). These range from simple biochemical tests such as measuring 17 hydroxyprogesterone levels to diagnose 21 hydroxylase deficiency, or more complex tests such as a chromosome analysis (karyotype) to diagnose Turner syndrome (45,X) or Klinefelter syndrome (47,XXY). More recently, molecular karyotyping involving array comparative genomic hybridization (aCGH) has become the first-line test to diagnose chromosome microdeletion/microduplication disorders [6]. Molecular testing typically involves looking for sequence changes within a gene, and can be done in one of several ways. The simplest test involves *targeted mutation analysis*, attempting to identify a specific mutation at a specific position within a gene, obviating the need to sequence the entire gene. This is typically done when the disease-causing mutation is known in a family member (the proband), and other relatives at risk are being screened. In some disor-

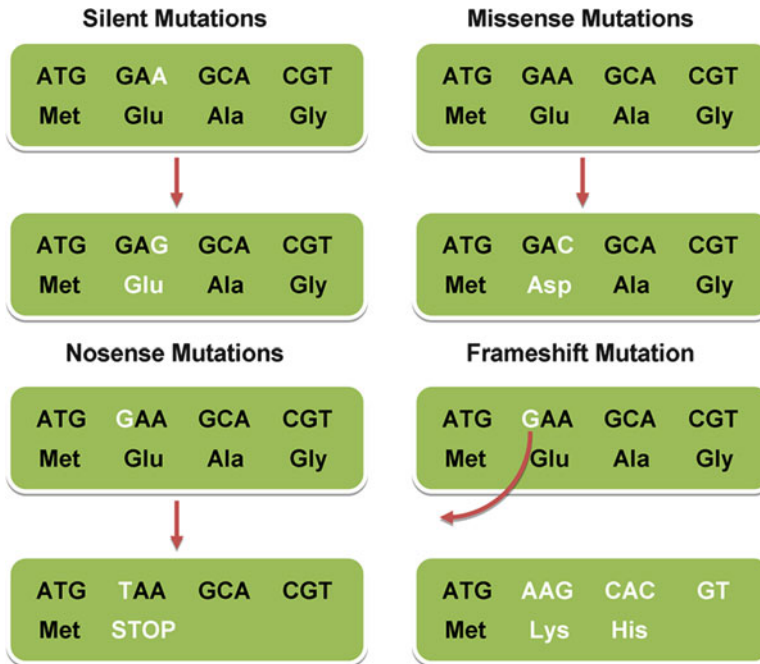


**Fig. 1.2** Structure and function of genes

ders, only a few mutations are responsible for the disease, and thus *mutation scanning* can be performed, which involves searching for those select mutations only. In most diseases though, mutations are scattered throughout the gene, and thus *sequencing* of all exons and intron–exon junctions to look for defects that may cause splicing errors needs to be performed. For some disorders, a small percentage of mutations are known to occur in regulatory regions, and these regions can be sequenced as well. It is important to remember that even the most comprehensive sequencing test will not pick up large deletions or duplications within a

gene, and thus techniques such as multiplex ligation probe amplification (MLPA) need to be performed in addition to sequencing.

Once molecular testing has been performed, the results have to be interpreted with caution, as this can sometimes be quite a complex undertaking. The test may be positive for a known disease-causing mutation, unequivocally confirming the diagnosis, or negative for a mutation, making the suspected diagnosis unlikely, depending on the clinical sensitivity of the test for that particular disorder. Not infrequently though, equivocal results are seen, making interpretation difficult. A variation may be seen in the DNA



**Fig. 1.3** Different types of point mutations

**Table 1.2** Types of genetic tests

- Biochemical testing
- Karyotype (chromosome analysis)
- Array comparative genomic hybridization (aCGH)
- Linkage studies
- Targeted mutation analysis
- Mutation scanning
- Sequencing
- Deletion/duplication analysis
- Genome-wide association studies
- Whole-exome or -genome sequencing

sequence that has not been described previously as a mutation, and that is neither described as a benign polymorphism (an inconsequential change in the DNA sequence that is part of normal human variation). Such a change is typically characterized as a variant of unclear significance (VUS), and a number of questions have to be answered to determine the clinical significance of the variant (Table 1.3). This includes determining whether the variant in the DNA sequence leads to a change in the amino acid sequence of the protein, or is a “silent” change that encodes the same amino acid. It is important to remember though that a “silent” change may lead to alternative

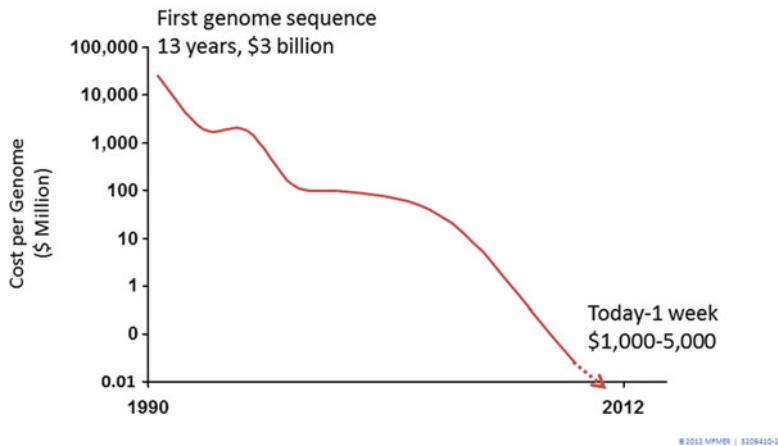
**Table 1.3** Factors to consider when evaluating a variant of unclear significance

- Silent vs. missense variant
- Effect on splicing
- Nature of amino acid change
- Degree of conservation of amino acid
- Frequency of variant in healthy population

splicing and thus could be pathogenic. The nature of an amino acid change (polar vs. nonpolar, bulky vs. small) and the degree of conservation of an amino acid through different species are also important factors in determining whether a variant is truly pathogenic or not. Another important factor to consider is the frequency of the variant in apparently healthy individuals, but this has been challenging due to lack of appropriate representation of ethnic minorities in biobanks collecting such information. Despite multiple computations, it may still be difficult to establish whether the particular variant is associated with disease or not.

The cost of DNA sequencing has dropped dramatically over the last few years, and next-generation sequencing techniques now make it possible to perform high-throughput testing quite

## Changing Cost of DNA Sequencing



**Fig. 1.4** The cost of DNA sequencing

efficiently (Fig. 1.4). It has thus become feasible to perform sequencing of the entire genome (coding and noncoding regions) or exome (coding regions only) in the clinical setting, although there are huge challenges in the interpretation of such vast amounts of data [7]. These challenges arise not only on the bioinformatics front but also on the ethical front, and a strong public debate is under way to help guide us on how best to use these new technologies in the clinical setting. Published examples of such *whole-genome* or *whole-exome sequencing* show that this is a novel approach to evaluate patients with suspected Mendelian disorders, where multiple genes may be implicated, or when the disease-causing gene/gene is/are unknown [8–10]. Bringing such type of testing to clinical practice still remains very controversial, not only because we simply do not know how to interpret the significance of the vast majority of variants that will be found by such testing but also because of the ethical considerations of incidentally finding mutations associated with currently untreatable disorders.

Over the last few years, a flood of data has been coming in from GWAS, attempting to identify genetic factors in common disorders such as T2DM [1, 2]. These studies are based on the fact that as part of normal human variation, all of us have multiple single-nucleotide polymorphisms

(SNP), occurring on average, at every 300 base pairs within the genome. SNPs that lie in close proximity to each other are likely to be inherited en bloc, and travel together down the generations. This allows for one SNP to act as a surrogate marker for another SNP, or possibly a mutation associated with a particular disease. GWAS are thus case–control studies looking at the presence or the absence of such SNPs in cases vs. controls. If there are adequate number of cases and controls (usually thousands), it is statistically possible to discern which SNPs are more likely to be present in cases vs. controls. If a few SNPs stand out, genes on which they occur or other genes in close proximity may be studied further to explore their role in the pathogenesis of that disorder. It is important to remember that most of these SNPs lie in noncoding regions, and thus may not be directly playing a role in the pathogenesis of a disease, but are merely surrogate markers for other DNA variants or mutations that lie in their proximity. Thus GWAS are hypothesis-generating studies, and should not be used in a predictive fashion. Unfortunately, since it is statistically possible to obtain an odds ratio (OR) for the occurrence of a certain SNP in cases vs. controls, certain commercial entities have been wrongfully marketing the use of this infor-

mation to predict disease in asymptomatic individuals.

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## Clinical Evaluation of Patients with Suspected Genetic Endocrine Disorders

Ideally, the endocrinologist should be able to partner with a medical geneticist or genetic counselor in the care of such patients. It is unfortunate though that outside of the tertiary care setting, access to a medical geneticist or genetic counselor remains quite limited, and the endocrinologist may thus have to navigate through the complex issues of genetic testing and its implications until the patient can be seen by a genetics provider. Endocrinologists will thus be faced with a number of questions they have to ask themselves when confronted with a patient who may have a heritable endocrine disorder. Some examples of such questions are given below:

1. In which clinical situations should a genetic syndrome be considered?

The key to making a clinical diagnosis of a genetic endocrinopathy is pattern recognition. This may not be difficult for some well-known endocrine syndromes, but it is hard to expect even the best clinicians to recognize a rare genetic syndrome every time. Multiple endocrinopathies in the same patient are usually the first clue. A focused three-generation family history often reveals a syndromic diagnosis, even if the patient has only one clinical finding. For example, asking a patient with a norepinephrine-secreting pheochromocytoma questions about a family history of renal cell carcinoma or CNS/retinal hemangioblastomas may betray a diagnosis of Von Hippel–Lindau (VHL) disease. Recognizing certain unusual clinical signs in association with an endocrine disorder is also essential to making a diagnosis. A patient with Cushing syndrome due to bilateral adrenocortical adenomas, who also has unusual brown pigmented spots on their skin (lentiginos), likely has Carney complex, and requires a cardiac echo to look for cardiac myxomas that could be life-

threatening if not resected. Using the open-access OMIM database (Online Mendelian Inheritance in Man, [www.omim.org](http://www.omim.org)) is very helpful, not only for looking up the cardinal features and inheritance pattern of a particular syndrome under consideration but also for searching to see if a combination of clinical features are part of a recognized genetic syndrome. OMIM is also linked to another useful website called GeneTests ([www.genetests.org](http://www.genetests.org)) which not only provides an up-to-date review on a number of genetic syndromes but also provides links to commercial and research laboratories performing genetic testing.

2. Is making a clinical diagnosis appropriate or does this have to be confirmed with genetic testing?

Genetic testing can be used to confirm a clinical diagnosis. Even if it is not essential for the diagnosis, if one is to identify presymptomatic individuals in the family who may benefit from screening, it is essential to confirm the presence of a pathogenic mutation in the proband, to ensure that accurate testing can be offered to family members at risk. In situations where the family history is not available (e.g., adoption) or the clinical scenario is not characteristic, genetic testing is essential in establishing a diagnosis. Results of genetic testing also direct management even if a clinical diagnosis is well established. A classic example is multiple endocrine neoplasia 2A (MEN2A), where the type of mutation in the *RET* proto-oncogene determines the age of onset of medullary thyroid cancer, directing the timing of prophylactic thyroidectomy in these individuals [11].

3. What is the sensitivity and specificity of genetic testing for a particular disorder?

Using the example of VHL again, the testing methodology entails both sequencing as well as deletion/duplication analysis of the *VHL* gene. Sequencing alone picks up approximately 70 % of cases, but would miss large deletions within the gene, which account for almost 30 % of cases [12]. Thus both tests together give a clinical sensitivity of >99 % but individually would not be sufficient to rule out the disorder. Some conditions, such as the

hereditary paraganglioma syndromes, are genetically heterogenous, and thus multiple genes have to be considered when attempting to confirm a diagnosis with molecular testing [13]. There may be as yet undiscovered genes associated with a particular syndrome. Thus limitations in both the testing methodologies as well as our understanding of the genetics of the disorder limit the sensitivity of most genetic tests today to well below 100 %. Results may reveal a VUS, and a novel change in the nucleotide sequence may not necessarily be pathogenic, making interpretation of test results challenging.

4. How expensive is genetic testing, and are there insurance and psychosocial implications of testing positive?

Even with considerable reduction in cost over the years, genetic testing still remains relatively expensive. The cost of an individual test may vary from lab to lab, but typically depends on whether a few mutations need to be detected, or whether the entire gene needs to be sequenced, the latter being a more expensive venture. The cost of sequencing also increases with the size of the gene and the number of exons being sequenced. Targeted mutation analysis might thus only cost a few hundred US dollars, but sequencing an entire gene may cost anywhere from \$1,000–3,000, although these costs will likely continue to decrease over the next few years. In most instances where genetic testing is essential to diagnosis or when it alters management, the cost of testing is covered by the insurer, but it is always best to get insurance pre-approval for such testing, since patients may be left with a significant out-of-pocket cost depending on their individual plan. For individuals who have clinical features of a disease, simply testing positive for a genetic disorder should not change their health insurability, but for presymptomatic individuals, there is a concern that genetic test results may have negative connotations. The Genetic Information Non-discrimination Act (GINA) has attempted to protect such individuals from the negative health insurance consequences, but there are

some important caveats, and currently does not include any protections from a life insurance perspective. For more details, please see [www.ginahelp.org](http://www.ginahelp.org). Finally, there are strong psychosocial implications of genetic testing, and consequences such as fear, loss of hope, and guilt are not unusual if patients test positive for a disorder. Thus it is strongly recommended that symptomatic and presymptomatic individuals receive nondirective pretest counseling, openly discussing the pros and cons of genetic testing prior to ordering the test.

5. What is the role of new genetic tests giving risk profiles to patients for common disorders such as T2DM?

T2DM, like most of the common disorders we deal with today, is a multifactorial disorder, having both genetic and environmental components. Even though the genetic contribution is quite significant, there most likely are multiple genes involved, each one contributing a small risk of disease. GWAS are attempting to identify such genes, to better understand the pathophysiology of the disease. As noted above, some commercial entities are marketing these tests directly to consumers, giving them risk profiles based on the presence or the absence of genetic variants. These data are not considered clinically relevant, unless further prospective studies validate these concerns. Looking at established clinical risk factors and the family history are better predictors of future onset of disease.

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## Summary

The clinical endocrinologist has to recognize clinical situations that warrant further consideration from a genetic standpoint. A focused family history and careful clinical exam will enable the astute clinician to recognize patterns that are reminiscent of an underlying heritable endocrinopathy. Decisions on whether genetic testing is needed should be made on a case-by-case basis, ideally with a medical geneticist or genetic counselor being involved from the outset. Interpretation of genetic test results can be chal-



lenging, and pretest counseling should be performed where all pros and cons of genetic testing are discussed with the patients prior to testing. Newer genetic tests are increasing our knowledge about the pathophysiology of endocrine disorders, but some may lack clinical validity and thus may not be useful in making clinical decisions. To provide the best care to our patients, we have to educate ourselves about the clinical validity and utility of new genetic tests becoming available today.

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# Hyperthyroidism and Thyrotoxicosis

# 2

Vahab Fatourechi

The term thyrotoxicosis applies to a clinical condition resulting from increased thyroid hormone action. It can result from excess thyroid hormone synthesis followed by release for which the term hyperthyroidism is applicable. Thyrotoxicosis can also result from a destructive process in the thyroid resulting in unregulated excess release of stored thyroid hormones without increased production [1, 2]. The thyrotoxicosis syndrome may also be due to exogenous source either iatrogenic or factitious. Hyperthyroidism is considered subclinical when mild increase in peripheral thyroid hormone levels, although within normal laboratory reference range, is in excess for that individual. Hypothalamus–pituitary axis senses the excess and the negative feedback mechanism results in suppressed or abnormally low thyrotrophic hormone (TSH). Thus it can be argued that this is a biochemical rather than a clinical term. Subclinical hyperthyroidism may be symptomatic or asymptomatic but in either case has adverse effects [3]. In the United States subclinical hyperthyroidism is more common (0.7 %) than clinical hyperthyroidism (0.5 %), however much less common than subclinical hypothyroidism (3–10 %). If biologic activity of thyroid hormones is reduced such as in thyroid hormone

resistance [4], increased peripheral thyroid levels do not result in thyrotoxicosis syndrome.

Thyrotoxicosis is a syndrome with many diverse etiologies [1]. When clinical symptomatology or biochemical findings establish excess thyroid hormone effect, diagnostic measures should be directed at finding the specific etiology, since management and therapy will depend on the etiology. Graves' hyperthyroidism is the most common cause of hyperthyroidism in the United States. Toxic multinodular goiter and toxic adenomas are the next common causes. Nodular toxic goiter is more common in older individuals and in geographic areas with historical iodine deficiency [5]. Inappropriate excess thyroxine (T4) therapy or T4 suppressive therapies for follicular cell-derived thyroid cancer are also common causes of subclinical hyperthyroidism.

The first step after establishing the diagnosis of thyrotoxicosis syndrome, if not contraindicated because of pregnancy or lactation, is to obtain a radioactive iodine uptake of thyroid. High radioactive iodine uptake (RAIU) in iodine-sufficient areas is consistent with Graves' hyperthyroidism and very rarely TSH-producing pituitary adenoma. Occasionally toxic nodular goiter may have mildly elevated uptake but usually uptake is normal and sometimes low [6]. In Graves' disease degree of elevated uptake is usually proportional to the severity of Graves' disease; subclinical cases may have normal uptake. Very low and near-zero RAIU is consistent with silent thyroiditis, subacute thyroiditis, postpartum thyroiditis, iodine-induced hyperthyroidism,

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drug-induced hyperthyroidism, or any cause of hyperthyroidism after iodine contrast studies or excess exogenous iodine consumption. Normal RAI uptake can be associated with mild or sub-clinical hyperthyroidism of Graves' disease or nodular toxic goiter.

Hyperthyroidism associated with Graves' disease is an autoimmune condition in which the pathogenesis of hyperthyroidism is stimulation of TSH receptors by TSH receptor antibodies (TRAB) [7]. Pathogenesis of extra-thyroidal manifestations such as ophthalmopathy and dermopathy is less clear. Interaction of TRAB with TSH receptors in non-thyroidal tissues is important in the pathogenic process [7, 8].

Recent extensive guidelines for management of various types of thyrotoxic conditions by American Thyroid Association (ATA)/American Association of Clinical Endocrinologists (AACE) is a good source review since recommendations are recent and problem oriented [2].

### **Presentation of Thyrotoxicosis State**

Thyrotoxicosis usually presents with weight loss despite an increased appetite. Common symptoms are also palpitation, decreased exercise tolerance and dyspnea, nervousness, heat intolerance and excessive sweating, tremor and irritability, sleep disorder, and muscle weakness of varying degree. In older individuals hyperstimulation and adrenergic symptoms are less marked and patients may be apathetic and complain of fatigue and weight loss or muscle weakness or the disease may present with cardiac findings such as atrial fibrillation or heart failure. Increased appetite may not be present in the older patients who often have anorexia. In younger patients occasionally increased appetite may prevent weight loss and in some cases actually weight gain can be seen [9]. Pedal edema can be present without heart failure because of vasodilation. Gynecomastia may be present in severe cases. Diarrhea is a feature but most patients may have only more frequent bowel movements. In the case of Graves' dis-

ease an enlarged firm thyroid may be present but some patients have normal size thyroid. In Graves' disease continuous bruits over thyroid may be audible and flow murmur of carotid or venous hum may also be present [10]. Onset of symptoms in Graves' disease is subacute over weeks, or months, whereas in multinodular toxic goiter it is slow and subtle over a longer period of time [10]. In the latter a palpable nodular goiter is present or may become visible after weight loss. Graves' disease may present with extra-thyroidal manifestations such as ophthalmopathy and thyrotoxicosis symptoms may develop later in some cases [7, 11]. Mild stare of the eyes may be present in severely thyrotoxic patients who do not have ophthalmopathy but is not a prominent sign in my experience.

### **Clinical Presentations of Thyrotoxicosis-Mimicking Other Conditions**

Severe proximal muscle weakness in individuals older than age 50 may result in neurology referral before diagnosis is made. Also, in the same age group, atrial fibrillation or congestive heart failure may result in cardiology consultation. Symptoms of thyrotoxicosis are similar to anxiety disorder and diagnosis is missed if thyroid dysfunction is not considered. In cases of postpartum thyroiditis, present 2–3 months after childbirth, symptoms in the mother can be attributed to poor sleep and newborn care, and thyroid diagnosis is often overlooked. Elderly patients commonly present with apathetic form and do not have the usual hyper-stimulated features. Thus diagnosis may be missed and malignancy or depression may be suspected. In patients presenting with diarrhea and weight loss malabsorption or gastrointestinal conditions will be in the differential diagnosis. Some patients may have hypercalcemia and differential diagnosis of hypercalcemia initially may be a consideration [10].

Laboratory studies may also be misleading. Suppressed TSH can be seen in pituitary problems, in euthyroid sick syndrome, and with medi-

cations such as high-dose corticosteroids. Elevated peripheral thyroid hormone levels can be seen in thyroid hormone resistance. If only total T3 and T4 levels are measured in cases with increased thyroxine binding capacity T4 levels will be high but TSH will be normal [10].

A hypokalemic periodic paralysis syndrome can occur with thyrotoxicosis [12]. It is more common in oriental patients and much less common in other ethnic groups [13]. A genetic predisposition is needed and attacks of paralysis are precipitated by high carbohydrate intake and exercise. Acute attacks should be treated with parenteral potassium administration. Management of hyperthyroidism should be urgent and definitive for achievement of euthyroidism by RAI or surgery [12]. Occasionally surgical thyroidectomy may be the best management.

## Thyrotoxicosis Syndromes

### Hyperthyroidism Associated with High Thyroid RAIU [5]

These conditions include Graves’ disease, TSH-secreting pituitary adenoma, trophoblastic disease because of stimulation of thyroid by HCG, TSH receptor-activating mutations, hyperthyroidism in pituitary thyroid hormone resistance, and occasional cases of nodular goiter specifically associated with relative iodine deficiency (Table 2.1).

**Table 2.1** Causes of thyrotoxicosis

Hyperthyroidism associated with elevated or normal thyroid radioactive iodine uptake
Graves’ hyperthyroidism <sup>a</sup>
Multinodular goiter or toxic adenoma TSH-producing pituitary adenoma <sup>b</sup>
Some cases of thyroid hormone resistance
Hyperthyroidism associated with trophoblastic disease
TSH receptor-activating mutations
Hyperthyroidism in some cases of McCune–Albright syndrome

<sup>a</sup>In mild cases RAI uptake may be normal

<sup>b</sup>Usually uptake is normal or occasionally low

**Table 2.2** Causes of thyrotoxicosis

Thyrotoxicosis associated with near-zero thyroid radioactive iodine uptake
Silent thyroiditis
Postpartum thyroiditis
Granulomatous (subacute thyroiditis or de Quervain’s)
Acute infectious thyroiditis
External beam radiation-induced thyroiditis
Extensive metastatic follicular cancer after thyroidectomy
Iatrogenic thyroiditis
Factitious thyroiditis
Struma ovarii
Bleeding into functioning thyroid nodule
Amiodarone-induced thyroiditis
Drug-induced and biotherapy-induced thyroiditis
Thyrotoxicosis from meat or sausage with high thyroid tissue contamination
Iodine-induced hyperthyroidism
Any hyperthyroid cause associated with exogenous iodine ingestion or iodinated radiologic contrast (depending on the cause uptake may be low but not near zero)

### Hyperthyroidism Associated with Normal RAIU

In all of the above conditions if of mild degree, in particular if hyperthyroidism is subclinical, uptake may be normal [5]. RAI uptake is usually normal in toxic multinodular goiter and toxic adenoma. Some cases of multinodular goiter may have low radioactive iodine uptake [6].

### Thyrotoxicosis Associated with Very Low or Near-Zero (Table 2.2) Neck RAIU [2, 5]

These include iodine-induced hyperthyroidism, silent thyroiditis [14, 15], postpartum thyroiditis [16], and any form of thyrotoxicosis associated with exogenous iodine. One rare cause is struma ovarii [17] when thyroid RAIU is very low and pelvic ultrasound followed by pelvic radioactive iodine scan will be diagnostic. Silent and postpartum thyroiditis have a similar course as subacute granulomatous thyroiditis but pain is not present and etiologies are either autoimmune

**Table 2.3** Medications commonly used in management of thyrotoxicosis

<i>Symptomatic therapy</i>		
Short-acting propranolol <sup>a</sup>	10–40 mg	TID–QID
Slow-release propranolol	70–240 mg	QD–BID
Atenolol <sup>b</sup>	25–100 mg	QD–BID
Nadolol <sup>c</sup>	40–160 mg	QD
<i>Antithyroid medications</i>		
Methimazole, starting dose <sup>d</sup>	10–40 mg/day	QD–BID
Methimazole, maintenance dose	5–20 mg/day	QD
Propylthiouracil (PTU), starting dose <sup>e</sup>	100–400 mg/day	TID
Propylthiouracil (PTU), maintenance dose	50–200 mg/day	BID–TID

<sup>a</sup>Propranolol is a nonselective beta-blocker and has the possibility of reducing T4-to-T3 conversion at high doses. It is contraindicated in asthma. Should be stopped when thyroxine levels normalize

<sup>b</sup>Atenolol is beta-1 adrenergic selective

<sup>c</sup>Nadolol is a nonselective beta-blocker and also has possibility of inhibiting T4–T3 conversion

<sup>d</sup>Methimazole has lower side effect profile than PTU and can be given once a day. It is the drug of choice except for first trimester of pregnancy

<sup>e</sup>PTU has higher rate of hepatic side effects, has to be given divided. Is the only antithyroid used in first trimester of pregnancy

[16] or drugs. Sedimentation rate will be normal and antithyroid antibodies will be positive. For diagnosis of silent thyroiditis absence of history of iodine intake and iodinated contrast studies are needed and for confirmation urinary iodine measurement is helpful. Transient thyrotoxicosis states are treated with nonselective beta-blockers such as propranolol (Table 2.3).

### Thyrotoxicosis with Low Thyroid RAIU and Low Serum Thyroglobulin

Iatrogenic and factitious thyrotoxicosis is associated with low RAIU [18]. In the presence of small thyroid size and thyrotoxicosis associated with very low thyroid RAI uptake and absence of iodine contamination, if factitious thyrotoxicosis is suspected a very low serum thyroglobulin should suggest exogenous factitious or inadvertent thyroid hormone intake, even if patient does

not volunteer the history. If thyroglobulin antibodies are positive it interferes with the assay and low thyroglobulin is not reliable. It should be noted that serum thyroglobulin may be normal if patient has preexisting nodular goiter concurrent with excess thyroid hormone intake. Consumption of hamburger and sausages containing thyroid has also been associated with exogenous thyrotoxicosis in some reported cases [19].

### Thyrotoxicosis Presenting with Neck Pain

There are three conditions that present with thyroid pain and thyrotoxicosis. The most common is granulomatous thyroiditis or de Quervain's thyroiditis [20], most likely a viral condition. It usually follows an upper respiratory infection, is associated with a febrile illness, and presents with exquisite thyroid pain and tenderness radiating to ears and very firm and irregular thyroid. One lobe can be involved first followed by the other. Thyroid hormone levels are elevated, TSH is suppressed, RAIU is close to zero, sedimentation rate is high, blood count is normal, and serum thyroglobulin level is elevated [14]. Condition is followed by a transient hypothyroid phase and less commonly (in 5–15 %) by permanent hypothyroidism. The process lasts few months. Management of thyrotoxicosis is by nonselective beta-blockers (Table 2.3) and nonsteroidal anti-inflammatory agents (NSAIDs) and in severe cases by a short course of corticosteroids. Recurrence may occur in 2–5 % after several years. Suppurative thyroiditis also presents with thyroid pain but has a different presentation and course.

The second cause of painful transient thyrotoxicosis is bleeding into a functioning nodule resulting in release of stored hormones. This will be unilateral with distinct palpable nodule. ESR is normal, radioactive iodine uptake is low, and serum thyroglobulin levels are extremely high. Diagnosis is by thyroid ultrasound. Symptoms are usually mild; pain has a short duration. Duration of hyperthyroidism is also shorter than subacute thyroiditis.

The third cause is rare association of thyrotoxicosis with suppurative thyroiditis. Bacterial infection of thyroid and abscess formation are rare. Infection may occur after procedures or spontaneously and also from infected piriform sinus fistula [21]. It is associated with fever and local inflammatory signs and symptoms and abnormal blood count. Diagnosis is with neck ultrasound showing abscess formation. Fine needle aspiration (FNA) and culture establish the infectious etiology. Thyrotoxicosis is usually short lived and may be masked by inflammatory and systemic symptoms [22]. Management is management of infection and beta-blocker for thyrotoxicosis symptoms.

### **Drug-Induced Thyrotoxicosis and Hyperthyroidism**

Iodine-containing contrast media can cause iodine-induced hyperthyroidism particularly in iodine-deficient areas and in patients with nodular goiter. The duration depends on the half-life of clearance of exogenous iodine. In case of radiologic contrast media usually it will be a few weeks or months; in case of amiodarone it is several months to a year. Lithium [23, 24], interferon gamma, interleukin-2, and anti-cytokine therapies and biotherapies can cause transient painless thyroiditis that lasts weeks to few months and should be managed with beta-blockers and supportive care. Sometimes thyroid autoimmunity such as Graves' disease is induced by these medications. Tyrosine kinase inhibitors and thalidomide derivatives may cause thyroid dysfunction and sometimes thyroiditis with transient hyperthyroidism [25].

### **Amiodarone-Induced Thyrotoxicosis**

This is one of the most difficult management problems in thyroidology [26]. Patients usually have a critical and sometimes life-threatening cardiac arrhythmia. Amiodarone has high concentration of iodine and after discontinuation of therapy may stay in the body up to 6–12 months.

Thyroid RAIU is not helpful for diagnosis because it is low due to a high iodine pool. Two types of thyrotoxicosis are recognized with amiodarone: Type I is iodine induced and more common in iodine-deficient areas. Type II, a toxic destructive thyroiditis, is the more common type. Type I occurs usually in the background of nodular goiter [26]. It is essential to differentiate these two types since therapies are quite different. Therapy of type I includes antithyroid drugs and discontinuation of amiodarone; therapy of type II is corticosteroids. Ultrasound of thyroid is helpful in differentiation of these two: In type II thyroid size is usually normal and thyroid is distinctly hypovascular [27]. The problem is that although 90 % of the cases are type II, many cases are mixed and thyrotoxicosis develops as a result of both release and increased production of hormones. Although pure type II should respond to corticosteroids within 2–5 weeks, sometimes combination empiric therapy with methimazole along with corticosteroids may be needed. Early response to corticosteroids and normalization of thyroid function within 2–5 weeks favor type II diagnosis. Amiodarone therapy should be stopped if possible, since iodine-induced type will continue and type II thyroiditis may recur. Some cases may not respond to medical therapy and in those surgery is a good option for rapid cure [26, 28, 29].

### **Subclinical Hyperthyroidism**

Subclinical hypothyroidism is defined by lower than normal serum TSH, not explained by other causes such as pituitary disease, medications and acute illness, and normal levels of T3 and T4 [3]. This condition is more common than overt symptomatic hyperthyroidism. Etiologies are similar to clinical hyperthyroidism and thyrotoxicosis. It is present in mild Graves' disease or early-stage autoimmune disease or in toxic nodular goiter. Approximately 50 % of subclinical hyperthyroidism cases have subtle symptoms such as increased pulse rate. Symptoms are usually absent if TSH is  $>0.1$  mIU. Younger individuals may tolerate

the condition without adverse effects but in postmenopausal women increased bone loss is the consequence. Individuals older than 60 years have three times higher likelihood of having atrial fibrillation [30]. There is some evidence from epidemiologic studies suggesting increased mortality with serum TSH <0.5. Thus persistent subclinical hyperthyroidism should be treated in this group [31]. Therapy depends on etiology. In cases of toxic adenoma or multinodular goiter resolution of subclinical hyperthyroidism is unlikely and definitive therapy with radioactive iodine or surgery should be recommended. More than one abnormal test over time is needed before intervention.

Transient causes such as silent and subacute thyroiditis can be managed by beta-blockers waiting for resolution. In subclinical Graves' disease antithyroid and RAI therapy are equally effective. In younger age group beta-blocker therapy alone or observation is acceptable [32].

### **Hyperthyroidism Associated with Pregnancy**

Differentiation of physiologic gestational thyrotoxicosis from hyperthyroidism in the first 3 months of pregnancy is important and often difficult [33]. Thyroid is stimulated by human chorionic gonadotropin (HCG), TSH may be low or even suppressed, and symptoms may also be misleading. Very high levels of free T4, presence of goiter, and positive TRAB are helpful for diagnosis. Preexisting Graves' disease may improve during pregnancy and may relapse after childbirth. Treatment of hyperthyroidism is PTU in the first 3 months because of teratogenic effect of methimazole [34] but after first trimester PTU can be switched to methimazole because of its lower side effect profile. Total T4 should be kept 1.5 times above the upper limit of normal and free T4 at the upper limit of normal to prevent fetal hypothyroidism. Surgery can be done only in the second trimester if there are adverse reactions to antithyroid therapies or large doses of antithyroids are required for control of hyperthyroidism [35].

Because TRAB cross placenta and can affect fetal thyroid, these antibodies should be checked in patients with current or previous history of Graves' disease or a history of neonatal Graves' or previous elevated TRAB. If TRAB is positive at 2–3 times above normal fetal thyroid should be monitored by ultrasound at 18–22 weeks and repeated every 4–6 weeks. Evidence of fetal hyperthyroidism is goiter, hydrops, advanced fetal bone age, increased pulse, and cardiac failure. In this case even if the mother is euthyroid on thyroxine therapy methimazole or PTU should be given with close monitoring. There is no evidence that subclinical hyperthyroidism has adverse effect in pregnancy for the fetus and mother; thus therapy is not recommended [35].

### **Hyperthyroidism in Trophoblastic Disease**

HCG and TSH have similarities in their structure and receptors. Thus in the first trimester of pregnancy TSH levels are low and have inverse relationship with HCG levels. Mild physiologic thyrotoxicosis by HCG stimulation may be present that may be more pronounced in hyperemesis gravidarum [35]. Very high levels of HCG in hydatiform mole and choriocarcinoma [17] can present with significant hyperthyroidism and even thyroid storm [36, 37]. Treatment is management of the trophoblastic condition.

### **Hyperthyroidism with Inappropriately Normal Serum TSH in TSH-Producing Pituitary Adenoma**

In the presence of inappropriately normal serum TSH with elevated thyroid hormone levels and symptoms of hyperthyroidism, laboratory artifacts such as heterophile antibodies and abnormal binding to proteins should be excluded, as should thyroid hormone resistance. An MRI of pituitary should follow. Elevated beta-subunit will be in favor of TSH-secreting pituitary adenoma causing hyperthyroidism. These cases are very rare [2].

## Hyperthyroidism in Thyroid Hormone Resistance

Most patients with generalized thyroid hormone resistance have elevated peripheral thyroid hormone levels and inappropriately normal serum TSH and are clinically euthyroid [38]. If there is pituitary thyroid hormone resistance or if the degree of resistance is higher in the pituitary than peripheral tissues hyperthyroidism may occur [39]. Diagnosis of this rare condition is difficult and should be guided by clinical evaluation surrogates of excess thyroxine effects such as sex hormone-binding globulin (SHBG) may be useful.

## Thyrotoxicosis Associated with “Café au Lait” Pigmentation and Fibrous Dysplasia (McCune–Albright Syndrome)

In this syndrome associated with polyostotic fibrous dysplasia and “café au lait” pigmentation, because of constitutive activation of G(s) alpha by inhibition of its GTPase, non-autoimmune hyperthyroidism may develop and may be associated with nodular goiter. In this rare syndrome treatment is surgery or RAI ablation. Remission with antithyroid medications does not occur.

## Non-autoimmune Hyperthyroidism Caused by Genetic Mutation of TSH Receptor

Germline activating mutation of TSH receptor is a rare cause of hyperthyroidism in infancy and childhood. Best treatment after preparation with antithyroid medications is surgery at appropriate age. In adult patients RAI therapy can also be considered [40]. Activating mutations can also result in toxic adenoma that may present in adulthood.

## Metastatic Follicular Cancer and Hyperthyroidism

Thyrotoxicosis is rarely a presenting picture in widespread metastatic follicular cancer.

Occasionally it may present after excision of the primary tumor and may resolve with radioactive iodine therapy or excision of bulky tumors. It also can present with T3 toxicosis because of high rate of conversion of exogenous T4 to T3 of the therapeutic administered T4 by tumor that expresses high di-iodinase.

## Hyperthyroidism Associated with Normal T4 and Elevated T3 (T3 Toxicosis)

It is doubtful that T3 toxicosis is a distinct entity [2]. In the early phase of hyperthyroidism only T3 elevation may be present and T4 elevation occurs later. It is conceivable that in iodine-deficient areas and in certain conditions more T3 than T4 may be produced. Patients with hyperthyroidism on antithyroid therapy and after RAI therapy may have normal free T4 and elevated free T3.

Patients on excess thyroid extract therapy also have T3 toxicosis which can be associated with normal or low free T4, suppressed TSH, and elevated free T3 levels. This is due to excess T3-to-T4 ratio in the commercial product. In patients with thyroid extract therapy measurement of peripheral hormones does not correlate with thyroid function status and TSH measurement is the definitive test for assessment of therapy.

## Laboratory Investigation of Thyrotoxicosis and Hyperthyroidism

Although the first and most sensitive test in the presence of normal pituitary function is serum TSH, yet it is only an indirect measure of thyroid function and when thyrotoxicosis is suspected circulating hormone levels such as free T4 and free T3 should be measured [2]. First, free T4 should be measured and, if normal, measurement of free T3 should follow. To differentiate between the two main categories, high and low RAIU thyrotoxicosis, thyroid RAIU should be measured next [2]. Thyroid scan usually is not needed except for cases of



nodular disease with hyperthyroidism [2]. Ultrasound is sometimes helpful in the differential diagnosis. Ultrasound identifies nodule size, number, and vascularity. Increased vascularity in a diffuse goiter suggests Graves' disease, whereas low vascularity is seen in cases of destructive thyroiditis such as amiodarone-induced hyperthyroidism [27]. Also in cases of Graves' disease associated significant conditions such as occult malignancy change the management. When there is doubt about the etiology and also for prognostic assessment, measurement of TRAB is helpful [8]. Thyroid-stimulating immunoglobulin assay, a bioassay, is more expensive and is being replaced by immunoassay of TRAB.

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### Management of Thyrotoxicosis and Hyperthyroidism

For transient conditions such as silent, subacute, and postpartum thyroiditis and all conditions associated with the release of stored thyroid hormones, symptomatic therapy with nonselective beta-blocker medications (Table 2.3) are adequate as noted previously [2]. Two major and common causes of hyperthyroidism, Graves' disease and multinodular toxic goiter, require more detailed discussion.

### Management of Graves' Hyperthyroidism

Nonselective beta-blockers, if not contraindicated, will improve most symptoms and can be continued until hormone levels are normalized by specific therapy [2]. Hyperthyroid patients may require relatively high doses and 120–240 mg/day of propranolol and equivalent other beta-blockers may be needed (Table 2.3). If beta-blockers are contraindicated, calcium channel blockers can be used [2].

Choice of modality of definitive therapy for Graves' hyperthyroidism should be based on severity of hyperthyroidism, patient preference, and age of the patient.

Pediatric patients deserve a 1–2-year course of antithyroid medication [41]. Longer term antithyroid therapies are also a possibility. Methimazole is the drug of choice for all patients especially for pediatric age due to recent reports of life-threatening liver toxicity with (propylthiouracil) PTU [41]. In pediatric patients if antithyroid medications are not tolerated surgical subtotal thyroidectomy would be an option. However, despite hesitancy to use in children, it should be noted that RAI therapy in pediatric group has not been associated with long-term adverse effects [42].

In adults, one of the three choices should be presented to the patient: antithyroid drugs, radioactive iodine therapy, or surgery [2]. None of these modalities address the basic autoimmune process in Graves' disease. A mild immunosuppressive action is suggested for antithyroid medications. Theoretically, and based on some studies, a near-total thyroidectomy eliminates the source of thyroid antigen the fastest. RAI therapy increases the release antigen in the first few months but if total thyroid ablation is done eventually the antigen source will be decreased hence resulting in decreased antibodies later on and there may be long-term theoretical benefit.

### Pros and Cons of Antithyroid Therapy

Antithyroid therapy for 18 months results in only a 50 % remission rate. This is an argument in favor of thyroid-ablative modalities such as RAI, in particular in older individuals and in patients with co-morbidities [2]. Patient should also be counseled about possible side effects of antithyroid therapy, such as skin allergy and a 1/1,000 likelihood of agranulocytosis and pancytopenia [43], liver toxicity particularly with PTU [44], and rare cases of ANCA-positive vasculitis and lupus-like syndrome [45]. However some patients who want to avoid lifelong thyroxine therapy after ablative therapies prefer to use antithyroid drugs. The majority of endocrinologists in the United States choose RAI therapy as the preferred definitive therapy in adults [2].

If antithyroid therapy is chosen, drug of choice is methimazole with a starting dose of 20–30 mg daily which can be given in once-a-day program [45]. Prior to initiation of therapy a blood count and white count with differential and liver function tests such as transaminase and bilirubin should be obtained [2]. When thyroid functions normalize with therapy, which is usually in 5–8 weeks, maintenance dose of 5–10 mg will be usually adequate. Therapy should be continued for 18 months and, at that point if thyroid function is normal, it can be stopped [2]. Under certain conditions and for patients with reduced life expectancy, nursing home patients, in pediatric age group, and if patient does not accept ablative therapy, antithyroid therapy can be continued for a longer period of time [2].

Monitoring of antithyroid therapy is by measurement of free T4 and liver function tests initially and TSH, free T4, and liver function tests thereafter periodically. Blood count does not seem to predict impending agranulocytosis since it can happen in between tests. Advising patient to stop medication in case of complications, fever, and sore throat and obtaining a complete blood count with differential at that point are more helpful [2]. It should be noted that hyperthyroidism can cause mild leukopenia and also abnormal liver function tests, hence the need for baseline studies. If initial transaminases are more than five times normal antithyroid therapy should not be initiated [2].

Minor skin reactions can be transient but significant skin allergies should result in discontinuing medications. At that point alternate therapies or switching to PTU should be considered. However because of cross-reactivity in case of minor skin reactions it may be best to choose RAI or surgery.

### **How to Manage Recurrence of Hyperthyroidism After 18 Months of Antithyroid Therapy?**

In adults, ablative therapy preferably RAI therapy, is recommended. For women with pregnancy planned in the next 6 months surgery may be a good choice. Surgery, with the availability of a

high-volume experienced surgeon, may be suitable for patients with large goiter who are at good surgical risk or have moderate-to-severe ophthalmopathy, with concern about worsening of eye disease after RAI [2]. Long-term antithyroid therapy may be considered in very old patients or in children. Patient preference also should be a factor in decision [2].

### **Radioactive Iodine Therapy (RAI) for Graves' Hyperthyroidism**

In some clinics this is the first choice for initial management of adults with Graves' disease who accept post RAI hypothyroidism. Women who have no intention of pregnancy for 9 months are also candidates for RAI therapy. Unavailability of a high-volume thyroid surgeon and failure of or intolerance to antithyroid therapy are also good indications for ablative radioactive iodine therapy. Obviously, pregnancy and lactation are absolute contraindication. However if RAI is given it should be with the intention of making the patient hypothyroid within 3–6 months and to be followed by lifelong thyroxine therapy. RAI should also be avoided in women who plan pregnancy in the next 6–9 months. The dose of RAI must be proportional to the size of thyroid and degree of thyroid RAI uptake. The weight of thyroid estimated by palpation, or volume measured by ultrasound, can be used. In our clinic, we usually give 200 micro-Curie per estimated gram of thyroid weight adjusted for 24-h RAIU. Some authors suggest a fixed dose of 370-MBq for smaller thyroids and 555-MBq for larger goiters; however hypothyroidism rate in a 12-month follow-up is 56 % for the lower dose and 71 % for the higher dose [46]. If same-day treatment is desired a 4- or 3-h [47] uptake can be obtained and 24-h uptake calculated. Prior PTU therapy reduces sensitivity to RAI and we give 250 micro-Curie per estimated gram of thyroid weight. Methimazole may not reduce sensitivity to RAI. RAI dose should not be underestimated since the desirable hypothyroidism will be achieved sooner with higher doses. In our clinic with the above program 90 % of patients will be

hypothyroid within 3 months. TSH and free thyroxine should be obtained in 2 months and if patient is not hypothyroid in 3 months.

### **Management Before and Immediately After RAI Therapy**

Beta-blockers given before and for 4 weeks after RAI therapy is usually adequate [2]. Patients with severe thyrotoxicosis and patients with cardiac failure or with fragile health can be prepared with 3–4 weeks of methimazole therapy to reduce thyroxine levels to a safe range [48]. Antithyroid therapy should be stopped 3–5 days before RAI and can be started 3–5 days after RAI and continued for 4 weeks. Thyroid storm is rare after RAI but worsening of symptoms if significant should be reported and appropriate measures such as adjustment of beta-blockers, stable iodine or short course corticosteroids.

### **Surgical Management of Graves' Hyperthyroidism**

Surgery with near-total thyroidectomy rendering patients hypothyroid and placing patients immediately on thyroxine therapy in the hands of experienced thyroid surgeon is a safe and effective treatment for Graves' disease [49]. It can be considered for patients with very large goiters or with associated nodular disease, for patients with suspicious nodules in the thyroid, and for patients not responding to antithyroid therapy that do not want or are not candidates for RAI therapy. Pediatric age group with failure or intolerance to antithyroid therapy [50, 51] are also candidates. Pregnant women with poor response to antithyroid therapy are also candidate for surgery in second trimester of pregnancy. Patients with significant ophthalmopathy may also be candidates for surgery since it has been shown that after surgery TRAB decrease, whereas they increase with RAI therapy alone in the first year [2]. There is also 15 % possibility of worsening of ophthalmopathy, 5 % being permanent, if cor-

ticosteroid therapy is not given for 2–3 months concurrently [52]. Thyroidectomy for Graves' hyperthyroidism should be done only by a high-volume endocrine surgeon.

### **Preparing Patients with Graves' Hyperthyroidism for Surgery**

Although mild cases can be prepared with beta-blockers and iodide (a few drops of Lugol's solution or 1–2 drops of SSKI three times a day for 10 days prior to surgery) [53], usually it is best to normalize thyroid function with methimazole prior to surgery. With these precautions postoperative thyroid storm can be avoided. Iodine reduces vascularity as well as release of thyroid hormones from the gland.

### **Management of Severe Hyperthyroidism and Thyroid Storm**

Severe life-threatening thyrotoxicosis can occur in patients with associated non-thyroid-related acute conditions such as infection, rarely after radioactive iodine therapy, abrupt cessation of antithyroid therapy in severe cases, thyroid or in non-thyroid surgery and in unrecognized and untreated patients [54]. Thyroid storm manifests by arrhythmia, heart failure, hyperpyrexia, dehydration, hypotension, vomiting, diarrhea, confusion, agitation, stupor, and occasionally coma [54]. This is a true endocrine emergency and should be managed in intensive care setting [2] with hydration, cooling, respiratory support, and management of arrhythmia and cardiac complications. Thyroid hormone synthesis should be blocked by high-dose antithyroids (60 mg of methimazole or 600 mg of PTU) followed by inorganic iodide drop to stop release. Intravenous corticosteroid therapy is usually needed. Plasmapheresis has been used effectively in some cases [55]. Some cases of severe hyperthyroidism at risk of thyroid storm, but not yet in crisis, can be treated with combination of above modalities in outpatient setting with close observation.

## Management of Toxic Adenoma and Toxic Multinodular Goiter

Comprehensive guidelines for management of toxic adenoma and toxic multinodular goiter are well outlined in the ATA and AACE guidelines [2]. In summary, surgery is more appropriate for larger toxic nodules, younger patients, patient desire for a rapid cure, desirability of less than 1 % incidence of postsurgical hypothyroidism as opposed to 3–20 % for radioactive iodine therapy and 100 % rate of cure of hyperthyroidism as opposed to 80 % for radioactive iodine [2]. Availability of experienced thyroid surgeon, absence of comorbid conditions, and increased risk of surgery should be taken into account. RAI on the opposite is more appropriate for older patients, smaller nodules in younger individuals, and desirability of low rate of hypothyroidism [2]. For multinodular goiter same factors should be considered. However, in multinodular disease the rate of hypothyroidism after thyroidectomy is 100 % and is low after radioactive iodine therapy [2]. Compressive symptoms and presence of nodules with risk of malignancy will be an indication for surgery. Antithyroid medications are not appropriate for nodular toxic disease except for individuals with decreased life expectancy or increased risk factors for other modalities. In general antithyroids are not recommended except for preparation for surgery or in some cases prior to radioactive iodine therapy. Beta-blockers are usually adequate pre-therapy and post-therapy for radioactive iodine and pre-therapy for surgery. For patients receiving RAI therapy isotopic thyroid scan should be available since nonfunctioning nodule will need FNA for confirmation of benign nature prior decision for RAI therapy [2].

## Management of Hyperthyroidism Associated with Ophthalmopathy and Thyroid Dermopathy

Management of hyperthyroidism in the presence of ophthalmopathy is a matter of debate [56].

Surgery, and to a lesser degree antithyroids, reduces the receptor antibody levels, whereas RAI if not given with concomitant corticosteroids may increase the TRAB in the first year. Tobacco cessation in smokers and rapid achievement of euthyroidism are essential [57]. In the absence of ophthalmopathy and in nonsmokers ATA guidelines recommend RAI therapy without concurrent corticosteroids. For mild ophthalmopathy and no risk factors for thyroid eye disease, ATA accepts all three modalities of therapy, but if radioactive iodine is chosen concurrent corticosteroid treatment is recommended. However, ATA recommends antithyroid therapy or surgery for moderate-to-severe and sight-threatening ophthalmopathy [2]. Ablative therapy by radioactive iodine or surgery eliminates source of thyroid antigen and may have theoretical long-term benefit on the course of extra-thyroidal manifestations but evidence is lacking.

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## Conclusions

Thyrotoxicosis is the general term for excess thyroid hormone action. Hyperthyroidism is when thyroid is producing and releasing excess hormones. The most common cause is Graves' hyperthyroidism, the next being toxic nodular goiter. There are also several rare causes of overproduction of thyroid hormones. In conditions when destructive process in the thyroid results in release of stored hormones the term thyrotoxicosis is a better term, since thyroid is not overproducing hormones. As opposed to hyperthyroid situations the second category which is associated with near-zero radioactive iodine uptake is a temporary process and only supportive symptomatic therapy is needed. For hyperthyroid overproduction category, either antithyroid medications or ablative therapies such as surgery and radioactive iodine are needed. Management of thyrotoxicosis syndromes should be tailored to the cause associated with autoimmune manifestations, age of the patient, and other clinical considerations.

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Subclinical hypothyroidism (SCH), defined as an elevation in thyroid-stimulating hormone (TSH) with a corresponding normal FT4 level, assumes that there is an intact hypothalamic-pituitary-thyroid axis and an absence of intercurrent illness. The values should also be reproducible over a 4–6-week period. The prevalence of SCH is much higher, reported to be anywhere between 4.3 and 9 % [1, 2], and is more common in women than men.

Primary hypothyroidism, where the defect is at the level of the thyroid gland itself, accounts for over 95 % of cases of overt hypothyroidism. The remaining 5 % are caused by secondary or tertiary hypothyroidism (defect at the level of the pituitary gland or the hypothalamus) or thyroid hormone resistance.

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## Primary Hypothyroidism

Primary hypothyroidism has several causes. The most common cause in the United States and other iodine-sufficient areas is chronic autoimmune thyroiditis or Hashimoto's thyroiditis.

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Histopathologic examination of the thyroid gland reveals diffuse lymphocytic infiltration, follicular destruction, and Hürthle cells. There is a polygenic susceptibility, with a known association between Hashimoto's thyroiditis and HLA-DR3 [5]. Other factors such as pregnancy, radiation exposure, and, as evidenced by animal studies, viral infections can also predispose to developing the condition [6].

The diagnosis is confirmed by the presence of circulating antithyroid peroxidase (TPO) antibodies but antibodies to thyroglobulin (TG) and the TSH receptor (TRAb) may also be present. The presence of TPO antibodies is 92 % sensitive and 93 % specific for the diagnosis of Hashimoto's thyroiditis in the right clinical setting [7].

A firm, moderate-sized goiter that moves freely on swallowing is the most common physical feature of Hashimoto's thyroiditis. Rarely, an atrophic gland is present, the end result of autoimmune destruction of the gland. The natural history of the untreated goiter is a slow enlargement over many years. When there is rapid, painful enlargement of the gland, thyroid lymphoma should be suspected and an expedient work-up should be performed.

Medications can affect thyroid function in several ways. Drugs that affect thyroid hormone synthesis and secretion include amiodarone and other iodine-containing drugs (including radiographic agents), lithium, perchlorate, and others (Table 3.1). Other drugs increase thyroxine requirements by either binding to exogenous

**Table 3.1** Medications that affect thyroid function

Drug	Mechanism
<i>Inhibition of thyroid hormone synthesis and secretion</i>	
Amiodarone	Inhibits type I and type II 5' deiodinase, leading to decreased T3 generation from T4
Iodinated contrast agents	Inhibit type I and type II 5' deiodinase, leading to decreased T3 generation from T4 Decrease hepatic uptake of T4 Inhibit T3 binding to its nuclear receptor
Thiocyanate, perchlorate	Inhibit iodide transport into the thyroid gland
Propylthiouracil, methimazole	Inhibit thyroid peroxidase; propylthiouracil additionally inhibits peripheral conversion of T4 to T3
Lithium	Inhibits iodide binding and thyroid hormone release
<i>Decreased absorption of exogenous thyroid hormone</i>	
Calcium compounds, sucralfate, aluminum hydroxide, ferrous compounds, cholestyramine, colesevelam, proton-pump inhibitors, H2 blockers	Bind to levothyroxine and reduce its absorption
<i>Increased T4 clearance</i>	
Rifampin	Induces hepatic microsomal enzymes
Phenobarbital, carbamazepine	Induce hepatic microsomal enzymes Compete with thyroid hormone binding to TBG Accelerate the conjugation and hepatic clearance of T4/T3
<i>Decreased TSH secretion</i>	
Dopamine, L-Dopa, bromocriptine	Increase T3 synthesis from T4 in the brain
Opiates	Block the breakdown of T3 in the brain
<i>Others</i>	
Estrogens, SERMs	Increase thyroid-binding globulin
Steroids	Influenced by dose, type, and route of administration of glucocorticoid. Inhibit deiodination of T4; suppress TSH secretion; increase in renal iodide clearance
Salicylates	Compete for thyroid hormone-binding sites on binding proteins
Thalidomide	Immune-mediated subacute destructive thyroiditis

thyroid hormone, e.g., calcium salts, sucralfate, and cholestyramine, or increasing its metabolism, e.g., rifampicin, carbamazepine, and phenytoin. Tyrosine kinase inhibitors such as sorafenib and sunitinib, which are approved for use in gastrointestinal stromal tumors and renal cell carcinoma, have been shown to cause hypothyroidism in up to 70 % of patients, a side effect directly related to length of therapy [8]. The proposed mechanisms vary slightly between the different agents and include destructive thyroiditis with a reduction in thyroid hormone synthesis by inhibition of thyroid peroxidase activity. In patients already on thyroxine therapy, requirements increase, an effect thought to be mediated

by type 3 deiodinase activity which increases the metabolism of T4 and T3 [9].

Medications that cause a reduction in TSH secretion, such as glucocorticoids, opiates, and dopamine agonists, are also implicated in causing hypothyroidism.

Worldwide, the most common cause of primary hypothyroidism is iodine deficiency with approximately two billion people at risk, particularly those living in mountainous areas due to persistent glacial runoff depleting iodine stores. Consumption of cassava which contains compounds metabolized to thiocyanate enhances the iodine-deficient state by inhibiting thyroid iodine transport. The World Health Organization and



the US Food and Drug Administration recommendations are a daily iodine intake of 150 µg/day for the general adult population and 200 µg/day for pregnant or lactating women.

Other forms of thyroiditis may also cause primary hypothyroidism. Subacute or granulomatous thyroiditis initially presents with neck pain and biochemical hyperthyroidism, and may be followed by hypothyroidism. In one study, about 10 % of patients developed permanent hypothyroidism, defined as an elevation in TSH lasting beyond 1 year [10]. Postpartum thyroiditis (PPT) may present with hyperthyroidism followed by transient hypothyroidism, hyperthyroidism alone, or hypothyroidism alone in about 50 % of cases, usually within 2–6 months after delivery. It is more common in women with TPO antibodies, which confers up to a 50 % chance of developing PPT [11]. Most patients are euthyroid within the first postpartum year, although permanent hypothyroidism is more likely to develop in women with higher TSH values and higher antibody titers [12].

Iatrogenic causes such as post-thyroidectomy or post-ablative hypothyroidism constitute another category of primary hypothyroidism. Hypothyroidism occurs within 2–4 weeks of total thyroidectomy owing to thyroxine's half-life of 7 days. Data from patients undergoing radioactive iodine therapy for Graves' disease indicate that the rate of subsequent hypothyroidism is largely dependent on the dose of radioiodine used; in the United States most patients are hypothyroid within the first year of treatment [13]. External beam radiation which exceeds 25 Gy also causes hypothyroidism, which may be gradual in onset.

Infiltrative processes including hemochromatosis, lymphoma, amyloidosis, and sarcoidosis are rare causes of primary hypothyroidism. They tend to present as progressive, painless bilateral enlargement of the thyroid gland, and are usually part of more widespread systemic involvement of the disease. Infection of the thyroid is rare as the gland is encapsulated, and has good blood flow and a high iodine content. However *Pneumocystis jiroveci* infection in

immune-compromised patients has been reported to cause enough destruction of the thyroid gland leading to inadequate thyroid hormone production [14].

Consumptive hypothyroidism is a rare disorder that was initially identified in infants with visceral hemangiomas. There is a marked elevation in deiodinase type 3 (D3) activity which results in the conversion of T4 to reverse T3 and T3 to T2. The condition is treatable medically with glucocorticoids and interferon α.

Congenital hypothyroidism affects 1:6,000 live births in the United States [15]. Infants with the disorder have little to no clinical features of hypothyroidism and they are detected largely through newborn screening programs in place since the 1970s. Thyroid dysgenesis is responsible for 85 % of cases, with the remaining being caused by defects in thyroid hormone production at every level. Worldwide, the commonest cause is thyroid ectopy which accounts for about two-thirds of patients with thyroid dysgenesis. Central congenital hypothyroidism is much rarer and may be missed by screening programs that utilize TSH only. These infants usually have other pituitary hormone deficiencies [16]. Transient hypothyroidism in infants can occur as a result of maternal iodine insufficiency, maternal TSH receptor-blocking antibodies, or exposure to antithyroid drugs; infants are rendered euthyroid once the offending agent (antibody or drug) is naturally cleared.

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### Central (Secondary and Tertiary) Hypothyroidism

Central hypothyroidism is caused by TSH deficiency from disorders of the pituitary gland or hypothalamus. It is usually accompanied by deficiencies of other pituitary hormones, and can vary in severity. About 15 % of the function of the thyroid gland is independent of TSH and therefore central hypothyroidism may be milder clinically than primary hypothyroidism. Central hypothyroidism may be caused by tumors, surgery, and infiltrative, inflammatory, or infective processes and medications.

## Generalized Thyroid Hormone Resistance

Thyroid hormone resistance is a rare, autosomal dominant disorder in which the majority of patients have a mutation in the TR-beta gene. This results in reduced T3-binding affinity at the level of the thyroid hormone receptor and a reduced response to T3. Two-thirds of patients have goiters, but their symptoms may be a mix of both hypo- and hyperthyroid complaints. There is an increased prevalence of attention-deficit disorder which is present in about 10 % of patients [17]. Laboratory testing shows an elevated free thyroxine with normal or slightly increased TSH levels—the disorder therefore has to be differentiated from a TSH-secreting pituitary tumor. Treatment with T4 or T3 may be beneficial in patients with symptoms of hypothyroidism.

## Physical Examination

Physical signs of hypothyroidism are notoriously nonspecific and vary according to the severity of the disorder. The use of sensitive thyroid assays has largely superseded the value of physical examination findings in making the diagnosis of thyroid dysfunction (Table 3.2).

**Table 3.2** Common physical examination findings in hypothyroidism

Skin	Puffiness of the periorbital tissues, hands and feet, and supraclavicular fossae secondary to myxedema, pallor from anemia, dry, coarse skin secondary to reduced sebaceous gland secretions, easy bruising, dry brittle hair and nails
Cardiovascular	Narrow pulse pressure, reduction in cutaneous blood flow leading to cool, pale skin, distant heart sounds (if pericardial effusion is present)
Gastrointestinal	Weight gain from fluid retention, abdominal gaseous distension (myxedema ileus)
Nervous system	Slowing of higher mental function including speech, slowing of the relaxation phase of tendon reflexes
Muscular	Slightly increased muscle mass due to interstitial myxedema, myoclonus

## Evaluation

Laboratory testing is essential for making the diagnosis of hypothyroidism due to the lack of sensitivity and specificity of clinical findings. The most sensitive, “gold standard” test is TSH using a third-generation chemiluminescent immunoassay, which has the advantage of being more sensitive at the lower range than the second-generation test. The free thyroxine (FT4) level will differentiate between overt and SCH. Equilibrium dialysis is the gold standard for the measurement of FT4; however direct measurement via ultrafiltration is the most widely used method. It can also be measured indirectly through the free thyroxine index (FT4 index). Total thyroxine levels are affected by conditions that increase binding protein (e.g., pregnancy and illness) and must therefore be interpreted with caution.

There is considerable debate about the upper limit of normal for the TSH reference range. Data from the NHANES studies has shown an age-specific distribution of TSH, with higher normal values being seen in the elderly [18]. This has led some groups to propose a lowering of the upper limit of normal particularly in younger individuals, but evidence that thyroid hormone replacement in this newly identified group is beneficial is mixed [19]. Controversy also continues regarding the benefits of thyroxine therapy in SCH, with some recommending treatment [20, 21] and others arguing against replacement therapy, particularly in the elderly [22].

The measurement of TPO antibodies may be helpful in determining the etiology of hypothyroidism or in predicting the likelihood of progression to overt hypothyroidism in patients with SCH.

Patients with hypothyroidism may have associated laboratory findings including an elevated creatinine kinase, hyponatremia, and elevated total and LDL cholesterol values.

Ultrasound of the thyroid gland is not routinely recommended, but may be useful to confirm the diagnosis of Hashimoto’s thyroiditis if the characteristic heterogeneous echotexture is seen.

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## Treatment

Treatment of hypothyroidism is with thyroid hormone replacement, and the goal of therapy is to restore both biochemical and clinical euthyroidism. Levothyroxine (LT4) is the preferred agent as it allows for prevalent physiologic mechanisms to maintain T3 production in peripheral tissues. It has a half-life of 7 days, and therefore dose titration should be done after about 6 weeks once equilibration is achieved. A TSH goal should be used to adjust the dose of therapy, except in patients without an intact hypothalamic-pituitary-thyroid axis, in which case FT4 is used. Patients with suspected glucocorticoid deficiency should be evaluated and treated prior to initiation of levothyroxine.

The typical daily dose of levothyroxine in a patient without endogenous thyroid function is about 1.6 µg/kg ideal body weight. Care should be taken when initiating treatment in elderly patients with angina, as thyroid hormone can increase myocardial oxygen demand. Therefore, a recommended starting dose of between 25 and 50 µg/day is preferred with titration by 12.5–25 µg every few weeks in this population. Patients with SCH also require a lower starting dose of levothyroxine.

Levothyroxine should be taken on an empty stomach, ideally separated from food by at least 1 h. Several medications may affect the absorption of thyroid hormone (Table 3.1), and patients should be educated to allow at least 4 h to pass after a meal prior to taking thyroid hormone. Gastric acid is required for complete absorption of thyroid hormone; in patients on acid-reducing medication, one strategy may be to administer the dose at night when there is higher basal secretion of acid in combination with a slower intestinal transit time [23]. In patients who are unable to adhere to a daily dosing regimen, once-weekly dosing of levothyroxine with a dose slightly higher than seven times the daily dose has been shown to achieve biochemical euthyroidism without significant side effects [24].

Commercially available desiccated animal thyroid preparations, usually porcine in origin, contain both T3 and T4. The ratio of T3 to T4 in these

preparations tends to be higher than the ratio found in humans, thereby leading to suprathysiologic T3 levels. Additionally, due to the nature of the product, monitoring and standardization of desiccated thyroid preparations are lacking, leading to difficulty in dose adjustment.

Monitoring of therapy should be performed every 6 weeks after any change in treatment is made, be it to the dose or the brand of medication [25]. Amongst generic levothyroxine formulations, there is some variation in bioequivalence despite adherence to FDA standards. Therefore, in the athyreotic patient particularly, many practitioners advocate using brand-name medication only. Once the ideal dose is achieved, monitoring can be done on an annual basis. Certain circumstances should prompt reassessment of thyroid function sooner, for example, pregnancy which can increase requirements by up to 50 % [26]. Conversely, women on androgen therapy for breast cancer require less levothyroxine, as do hypothyroid patients in general as they get older. Many medications can interact with thyroid hormone absorption and metabolism (see Table 3.1) and these potential interactions should be kept in mind.

In some patients, despite achieving biochemical euthyroidism, hypothyroid symptoms such as fatigue and weight gain persist. The thyroid gland is responsible for 20 % of the body's T3 secretion with the remainder derived from peripheral conversion of T4 to T3. The theory of, therefore, supplementing the athyreotic patient with T3 in order to restore "physiologic balance" is an appealing one. Several studies have looked at whether a replacement strategy with both LT4 and triiodothyronine (LT3) results in better outcomes. An early positive study showed improvement in mood and neuropsychological parameters in these patients, but was criticized for its small number of patients, excessive use of thyroid hormone, and short follow-up [27]. Several subsequent, more rigorous studies and a large meta-analysis failed to replicate those results [28, 29]. More recently, a crossover study comparing thrice-daily dosing of LT3 in combination with LT4 versus LT4 alone demonstrated a modest but significant decrease in body weight, total cholesterol, and LDL cholesterol in the combination

group [30]. However this was a small cohort that was studied as in-patients for 6 weeks to ensure compliance with the regimen. This may be difficult to implement into practice for the general population, until perhaps a sustained-release preparation of LT3 is available.

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### Special Populations: Subclinical Hypothyroidism

SCH is a diagnosis made in a patient with an elevated serum TSH level and normal serum free T4. Symptoms may be vague and nonspecific or similar to those with overt hypothyroidism. Its prevalence increases with age and it is more common in women and in iodine-sufficient areas [31].

There are certain circumstances that need to be excluded prior to making the diagnosis. In a patient recovering from a non-thyroidal illness, there may be a transient increase in TSH. Similarly, often after the hyperthyroid phase of thyroiditis there can be a transient period of hypothyroidism. There is also a diurnal variation and a nocturnal surge in TSH with the highest values being seen in the morning. Hence, the diagnosis of subclinical hypothyroidism should only be made in a patient in whom the biochemical abnormalities are reproducible after about 6 weeks, and in whom there is an intact hypothalamic-pituitary-thyroid axis with no intercurrent illness.

The risk of progression from SCH to overt hypothyroidism is determined by the magnitude of TSH elevation and the presence of TPO antibodies [32]. In women with both high TSH values as well as high antibody concentrations, the cumulative incidence of hypothyroidism has been reported to be as high as 55 % [33]. Conversely, normalization of TSH values occurs more frequently in people with concentrations of 4–6 mU/L [34]. The underlying etiology for SCH also influences the rate of progression to overt hypothyroidism. For example, patients who recently received radioiodine therapy or external beam radiation are more likely to progress to overt hypothyroidism than patients who received external beam radiation as children.

There is inconsistent data regarding the risk of cardiovascular disease, neuropsychiatric symptoms, and mortality rates in patients with SCH with studies demonstrating both an increased and decreased risk of each outcome measure.

Current guidelines recommend treating patients with a TSH of >10 mIU/L and those with positive TPO antibodies as they have a higher risk of progression to overt hypothyroidism [35]. Additionally pregnant women or women contemplating pregnancy should also be treated [36]. More unclear is the benefit of treating patients with TSH between 5 and 9 mIU/L. SCH might be associated with greater cardiovascular risk in young and middle-aged people than in those older than 65 years, and therefore treatment may be justifiable in this group [37]. Levothyroxine therapy has been shown to improve surrogate cardiovascular endpoints such as carotid intimal thickness, endothelial function, and left ventricular function in several studies but the mortality benefit may only be seen after prolonged therapy [38]. Symptomatic patients with TSH values between 5 and 9 mIU/L may benefit from treatment, although studies show the effects to be greatest in patients with TSH >10 mIU/L [39].

The goal of therapy should be to bring TSH to the lower range of normal (0.5–3.0 mIU/L) in patients <65 years of age, and between 3 and 4.5 mIU/L in patients >65 years of age.

In patients who do not clearly qualify for therapy, monitoring thyroid function every 6–12 months is a reasonable strategy.

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### Special Populations: Hypothyroidism and Pregnancy

Pregnancy results in a twofold increase in thyroid-binding globulin and stimulation of the TSH receptor by  $\beta$ -HCG, an effect that wanes with decreasing production of  $\beta$ -HCG as the pregnancy progresses. Therefore the recommendation by the American Thyroid Association that there should be trimester-specific reference ranges for TSH in pregnancy has a sound physiologic basis, but is not widely practiced by commercial laboratories [40].

This phenomenon has impacted the definitions of overt and subclinical hypothyroidism in pregnancy. Overt hypothyroidism is defined as having a TSH of  $>2.5$  mIU/L with a corresponding trimester-specific low FT4 or a TSH of  $>10$  mIU/L regardless of FT4 levels. SCH is defined as having TSH between 2.5 and 10 mIU/L with a normal FT4 level. About 10–20 % of all pregnant women are TPO antibody positive and biochemically euthyroid. These women are more likely to have a TSH level that is  $>4.0$  mIU/L by the third trimester and up to half will develop PPT [41].

Overt hypothyroidism in pregnancy, if left untreated, may result in adverse maternal and fetal outcomes including preterm delivery, low birth weight, miscarriage, increased risk of fetal loss, and gestational hypertension [42, 43]. The data in women with SCH with or without thyroid autoantibodies also shows an increase in adverse pregnancy outcomes [44, 45]. However, there is less clear evidence that the neurocognitive development of the fetus is affected in women with untreated SCH [40, 46].

Thyroid autoimmunity itself may predispose to adverse fetal outcomes. In recent meta-analyses looking at euthyroid women with thyroid autoantibodies, there was a twofold increase in the rate of both spontaneous miscarriage and preterm delivery [47, 48]. The current ATA recommendation is to treat all pregnant women with overt hypothyroidism. There was no consensus regarding the treatment of women with SCH, although the argument for treatment may be more compelling in those with positive autoantibodies. If the decision is made not to treat women with SCH or thyroid autoimmunity, then monitoring thyroid function every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation is a reasonable strategy.

Women with preexisting hypothyroidism will likely require an increase in their dose of hormone replacement by up to 50 % until delivery [49]. The dose of levothyroxine should be increased by about 30 % as soon as pregnancy is confirmed, and titrated to maintain a

**Table 3.3** Target populations for TSH screening during pregnancy

Women at high risk for overt hypothyroidism during pregnancy
History of thyroid dysfunction, postpartum thyroiditis, or prior thyroid surgery
Age $>30$ years
Symptoms of thyroid dysfunction or biochemical features suggestive of thyroid dysfunction including anemia, hypercholesterolemia, or hyponatremia
Presence of goiter
TPO antibody positivity
Type 1 diabetes or other autoimmune disorders
History of infertility, miscarriage, or preterm delivery
History of head or neck radiation
Family history of thyroid dysfunction
Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
Residing in an area of known moderate-to-severe iodine insufficiency
Body mass index $\geq 40$ kg/m <sup>2</sup>

trimester-specific normal TSH. Practically speaking, this can be achieved by adding two extra doses of levothyroxine a week, i.e., nine doses, from seven. Ideally, preconception TSH should be  $<2.5$  mIU/L to achieve the most favorable outcomes during pregnancy. Serum TSH should be monitored every 4 weeks in the first half of pregnancy and at least once between 26 and 32 weeks gestation. In the absence of laboratory-specific ranges, it is reasonable to use the following upper limits of normal for TSH: 2.5 mIU/L in the first trimester, 3.0 mIU/L in the second trimester, and 3.5 mIU/L in the third trimester [36]. Postpartum, the patient should return to her pre-pregnancy dose of levothyroxine and a serum TSH should be checked about 6 weeks later.

Experts currently recommend against universal TSH screening of all pregnant women in the first trimester of pregnancy. Clinical practice guidelines instead advocate a “case-finding” approach and recommend certain high-risk groups of women have their serum TSH checked at the confirmation of pregnancy (Table 3.3) [40, 50]:

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## Special Populations: Myxedema Coma

Myxedema coma is the result of severe untreated hypothyroidism and manifests as hypothermia, generalized slowing of all organ functions, and decreased cognition. It is a medical emergency with a high mortality rate if left unrecognized and untreated. It can be a result of long-standing untreated hypothyroidism, or may be precipitated by exposure to cold, infection, trauma, or central nervous system depression particularly in the elderly population.

The typical patient will present with a history of known hypothyroidism and slowly worsening mental status changes. It is usually accompanied by a variety of clinical features which, at its most severe, can include hypothermia, hypotension, bradycardia, hyponatremia, hypoglycemia, and hypoventilation. The myxedema is a result of abnormal mucin deposition in the tissues and manifests as non-pitting edema of the face, tongue, and peripheries. Pleural, pericardial, and peritoneal effusions are not uncommon. Seizures may be present, partially due to hyponatremia which is present in about 50 % of patients [51].

The diagnosis should be considered in the hypothyroid patient who presents with compatible clinical features, and is confirmed biochemically. Serum TSH, free T4, and cortisol levels should be drawn prior to administering therapy. The majority of patients will have primary hypothyroidism, but an inappropriately normal TSH in the setting of a low free T4 would indicate a pituitary or a hypothalamic cause.

Treatment should be commenced even before biochemical confirmation of the diagnosis due to the high mortality rate of the condition. Severe hypometabolism can impair drug absorption from the gut, and so medications should be administered intravenously. Thyroid hormone replacement with both T4 and T3 is widely practiced as T3 has a faster onset of action and there is unpredictable T4-to-T3 conversion in the setting of severe hypothyroidism and concurrent non-thyroidal illness. A single loading dose of 400–500 µg of levothyroxine intravenously is initially given to replete the peripheral pool; this is converted to a

daily dose of 1.6 µg/kg thereafter. The loading dose should be lowered in the elderly and in patients with cardiovascular disease. T3 may be administered simultaneously, with or without a loading dose, at a dose of 2.5–10 µg every 8 h. Care must be taken to ensure that T3 levels are monitored appropriately as high levels have been shown to increase mortality [52]. Once the patient is able to tolerate oral medications, thyroid hormone replacement can be done orally at a dose of about three-quarters of the intravenous dose.

Glucocorticoids at stress doses should also be given until the diagnosis of adrenal insufficiency can be excluded. Additionally, supportive treatment, electrolyte monitoring, and treatment of any precipitating illness must be instituted. Hypothermia is best managed with passive warming as active warming may cause redistribution of blood flow to subcutaneous tissues and cardiovascular collapse. Hypotension generally resolves with thyroid hormone replacement over hours to days, but vasopressor support may be required temporarily.

Poor prognostic factors include increased age, reduced consciousness, persistent hypothermia, and sepsis. However, with expedient treatment, the mortality rate approaches that due to sepsis alone [53]. The key to successfully managing myxedema coma remains having a keen clinical suspicion for the condition and the prompt institution of thyroid hormone replacement.

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## Special Populations: Hashimoto's Encephalopathy

The first patient with co-existing autoimmune thyroid disease and intermittent seizures, disorientation, and EEG abnormalities was described in 1966. The etiological link between the thyroid dysfunction and neurological abnormalities however was not proven at that time and it has remained a controversial issue since. Hence, the term “Hashimoto's encephalopathy” is often bypassed for the more accurate “corticosteroid-responsive encephalopathy associated with thyroid autoimmunity” or “autoimmune encephalopathy associated with Hashimoto's thyroiditis” [54].

The condition is characterized by cognitive impairment, behavioral changes, and focal or generalized seizures. Many other neurological manifestations such as movement disorders, sensorial clouding, stroke-like symptoms and hallucinations have also been reported. In 2005, Chong and colleagues proposed that the diagnosis could be made in a patient with confusion, no cerebrospinal fluid (CSF) evidence of bacterial or viral infection, and a high serum titer of antithyroid antibodies [55]. Almost all patients have a nonspecific generalized slowing of background activity on electroencephalogram testing [56].

The patients reported in the literature have either had a known diagnosis of Hashimoto's thyroiditis or SCH or been positive for antithyroid antibodies. The neurological manifestations can occur even when the patient is biochemically euthyroid and there seems to be no correlation between the severity of thyroid dysfunction or levels of antithyroid antibodies and the degree of severity of neurologic symptoms [57].

The most common CSF finding is an elevated protein level, but there are some reports of antithyroid antibodies detected in CSF as well [58]. This has been used as indirect evidence to support a potential causal link between autoimmune thyroid disease and encephalopathy. Ultimately, the diagnosis of Hashimoto's encephalopathy is one of the exclusions, and other causes of delirium or rapidly progressive dementia should be screened for and ruled out.

A clinical response to immune modulators, in particular glucocorticoids, is a hallmark of the condition. Both oral and intravenous steroids have been used with good outcomes, and the time to meaningful recovery has been reported anywhere from several months to as long as 2 years. A relapsing course is not rare, but tends to respond to intensified steroid therapy [59]. Other immune-modulatory agents such as azathioprine, methotrexate, cyclophosphamide, and immunoglobulin have been used with variable success [60]. Thyroxine therapy alone does not improve neurological symptoms.

There is sufficient evidence from pathological studies and the response to immunomodulation that the neurological manifestations of this condition have an autoimmune basis. However, whether

coexistent thyroid autoimmunity represents causality or whether it is yet another manifestation of autoimmunity per se is still a matter of debate. Conversely, it remains to be seen if patients with thyroid autoimmunity are at higher risk for the development of autoimmune encephalopathy.

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## Introduction and Clinical Importance

Thyroid nodules are very common in clinical practice. The prevalence of thyroid nodules by palpation only ranges from 3 to 7 % [1] but it increases up to 76 % when evaluated by ultrasound [2]. Usually patients with clinical palpable thyroid nodule on physical examination are found to have additional nodules on US investigation [2, 3]. The estimated annual incidence of thyroid nodules is 0.1 % per year, suggesting that more than 300,000 new nodules will be detected this year, conferring a 10 % lifetime probability for developing a thyroid nodule [4, 5]. Thyroid nodules are more common in elderly persons, in women, in areas with iodine deficiency, and with a history of childhood radiation exposure [3, 6].

The main clinical importance of these nodules is the risk of malignancy. The majority of nodules are benign; approximately 5 % are malignant [5]. One recent study showed an increase in the thyroid cancer incidence to 8.47 per 100,000 in 2002 in the USA [7]. The preva-

lence of nodular thyroid disease is high so the main purpose of thyroid nodule evaluation is to determine which nodules are malignant or require surgical intervention.

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## History and Physical Examination

Clinical evaluation begins with a complete medical history and thyroid palpation. Both benign and malignant disorders can cause thyroid nodules (Table 4.1). Attention should be directed to information on previous history of radiation treatment of the head and neck, rate of growth of the mass (location, size and consistency), associated cervical lymphadenopathy, local symptoms (pain, dysphonia, dyspnea, or dysphagia), and other associated symptoms of hypothyroidism or hyperthyroidism. Most patients will have few to no symptoms during evaluation as the majority of thyroid nodules will be discovered incidentally. Malignancy rate in younger and older patients are increased threefold to fourfold when compared to adults [8, 9].

Family history should be obtained, paying special attention to a history of medullary thyroid carcinoma (MTC), papillary thyroid carcinoma, multiple endocrine neoplasia types 2A and 2B, familial polyposis disease, Cowden disease, Carney complex, Gardner syndrome, and other rare diseases [10–13]. Table 4.2 shows findings suggestive of increased risk of malignancy potential.

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**Table 4.1** Common causes of thyroid nodules

Benign nodular goiter
Thyroiditis
Cysts
Primary thyroid cancer
Papillary carcinoma
Follicular carcinoma
Hurtle cell carcinoma
C-cell derived carcinoma, Medullary carcinoma
Anaplastic carcinoma
Metastatic Cancer
Lymphoma

**Table 4.2** Findings of increased malignancy potential

Prior history of head and neck irradiation
Family history of MTC, MEN type 2, PTC, or other syndromes
Age <14 or >70 years
Male sex
Growing nodule, firm or hard consistency, fixed
Cervical adenopathy
Persistent dysphonia, dysphagia, dyspnea, or vocal cord paralysis

## Diagnostic Evaluation

### Serum Markers

Besides a complete history and physical exam all patients should undergo a serum TSH level measurement [14, 15]. If the TSH is low a thyroid scintigraphy should be performed to determine the functional status of the nodule as low TSH suggests overt or subclinical hyperthyroidism, hyperfunction (“hot”), and autonomous functioning adenoma. If indeed the nodule is found to be “hot” it is unlikely to be malignant and FNA should be deferred [16].

On the other hand, a low TSH can be secondary to Hashimoto’s thyroiditis and these patients can also present with a “pseudonodule” due to focal lymphocytic infiltration. TPO antibodies can be helpful in the diagnosis. In this case abnormal thyroid function does not exclude thyroid cancer and if a true nodule is found further investigation is needed. TSH levels are independent predictors of malignancy in patients with thyroid

nodules: the risk of malignancy increases as the TSH levels also increases [17, 18].

Calcitonin is a marker for detection of C-cell hyperplasia and MTC, and levels >10 pg/mL have high sensitivity for the detection of MTC. Calcitonin should be measured in patients with family history of or high clinical suspicion of MTC or MEN 2 syndromes. Overall, the prevalence of MTC cancer in the USA is low and current ATA guidelines do not recommend “either for or against routine measurement” [14]. On the other hand, AACE guidelines state that measurement of basal serum calcitonin “may be useful as initial tool for evaluation of thyroid nodules” [15].

Other tests including serum calcium, PTH, serum thyroglobulin are neither sensitive nor specific so they are currently not recommended as routinely for the initial evaluation of thyroid nodule [14].

### Imaging Studies: Ultrasound

Ultrasonography, more sensitive than palpation, is the imaging of choice to detect thyroid nodules. Thyroid ultrasound (US) should be performed in all patients with a suspected thyroid nodule, a goiter, or after an incidentally found nodule by other imaging modalities. Thyroid US is noninvasive, inexpensive, has a sensitivity of 95 % and can identify nodules usually not palpated on the physical exam. Ultrasound provides a very good evaluation of nodule size, dimensions, structure, and any possible suspicious features. It can also differentiate solid from cystic nodules [14, 15, 19].

Several US features can be suggestive of malignancy: microcalcifications, irregular borders, hypoechogenicity, taller-than-wide shape, and increased vascularity. These characteristics have high specificity but the positive predictive value is lowered by their relatively low sensitivity [20–22]. See Table 4.3 for details. None of these features alone is enough to differentiate a benign from malignant lesion [23]. Findings such as isoechogenicity and spongiform appearance are features of benignity [22]. Suspicious cervical adenopathy without hilus, cystic changes,

**Table 4.3** Predictive value of ultrasonographic features in detection of thyroid cancer

Ultrasound feature	Sensitivity (%)	Specificity (%)
Microcalcifications	52 (26–73)	86 (69–96)
Absence of halo	66 (46–100)	54 (30–72)
Irregular margins	55 (17–77)	79 (63–85)
Hypoechoogenicity	81 (49–90)	53 (36–66)
Increased vascularity	67 (57–74)	81 (49–89)

Adapted and reproduced from Fish et al. [63]

microcalcifications, and hypervascularity have a high probability for malignancy [24]. Complex nodules with solid and cystic components often with a dominant cystic part are frequently benign.

Numbers of nodules and size are not predictive of malignancy. In a gland with multiple nodules the selection for FNA should be based on the US features rather than size alone. Cancer is not less frequent in small nodules so diameter cutoff alone to evaluate cancer risk is not recommended [20, 25].

Screening of thyroid nodules by US or any other type of images is not recommended in the general population due to slow growth and minimal aggressiveness of thyroid cancers. Ultrasound should only be performed in patients with known or suspected thyroid nodules or presence of risk factors [14]. Advances in diagnostic imaging have improved the management of thyroid nodules, but it is also associated with the discovery of very small thyroid nodules (incidentalomas) of questionable and indeterminate clinical importance.

### Imaging Studies: Others

Other techniques like MRI and CT scan are not recommended as routine tests as they are expensive and rarely diagnostic. CT scan and MRI have more value to assess size, substernal extension or extension to surround structures. Iodine contrast should be avoided as it decreases subsequent iodine 131 uptake [15]. Thyroid scintigraphy should be performed when there is suspicion of autonomy of the nodule (low TSH) suggesting overt or subclinical hyperthyroidism.

### Fine Needle Aspiration Biopsy

Ultrasound-guided fine needle aspiration (FNA) is the procedure of choice in the evaluation of thyroid nodules and is the most accurate test for determining malignancy [4, 14, 15]. It is safe, cost-effective, and preferred over palpation-guided leading to much lower rates of nondiagnostic and false-negative cytology results [26].

Biopsy may cause mild, transient pain or hematoma. Neither other serious adverse effects nor seeding of tumor is reported [4]. Ultrasound guidance is very helpful in selecting the proper target for FNA, especially when nodules are <1 cm, cystic or impalpable. In multinodular goiters, if nodules have benign sonographic appearances, often FNA of the largest nodule may be sufficient. When performed by experienced physicians, adequate sample can be obtained from solid nodules in 90–97 % of aspirations [26]. There is no single ultrasound characteristic of malignancy but instead a combination of features that need to be evaluated as predictors of malignancy [4].

### Cytology

Thyroid FNA slides should be reviewed by a cytopathologist with experience in thyroid. FNA has reduced the number of surgical procedures in patients with nodules by more than 50 % and substantially increased the malignancy yield at thyroidectomy [27]. An adequate sample is highly accurate for diagnosing thyroid cancer. Biopsy results may be classified as satisfactory or unsatisfactory (non-diagnostic). To be considered diagnostic or satisfactory the aspirate needs to contain no less than six groups of well-preserved thyroid epithelial cells consisting of at least ten cells in each group [28].

The new Bethesda FNA classification has five diagnostic categories: benign (70 %); malignant (5 %); and suspicious for malignancy including follicular or Hürthle cell neoplasm, follicular lesions of undetermined significance or atypia, representing 25 %. See Table 4.4 for details [28].

Overall, 10 % of the FNAs will be unsatisfactory (non-diagnostic), usually because of sampling error or poor technique. Biopsy should be

**Table 4.4** The Bethesda system for reporting thyroid cytopathology: implied risk of malignancy and recommended clinical management

Diagnostic category	Risk of malignancy (%)	Usual management
Nondiagnostic or unsatisfactory	1–4	Repeat FNA with ultrasound guidance
Benign	0–3	Clinical follow-up
Atypia of undetermined significance or follicular lesion of undetermined significance	5–15	Repeat FNA
Follicular neoplasm or suspicious for a follicular neoplasm	15–30	Surgical lobectomy
Suspicious for malignancy	60–75	Near-total thyroidectomy or surgical lobectomy
Malignant	97–99	Near-total thyroidectomy

Bethesda System; adapted from Baloch et al. [28]

repeated but approximately 7 % of these nodules will still be unsatisfactory [14, 29–32]. The false-negative result range from 1 to 11 % but usually will be less than 5 % in most clinics with enough FNA experience [31, 33].

## Management, Therapy, and Follow-up

### Benign Thyroid Nodule

The most common benign lesions include colloid nodule, macrofollicular adenoma, benign cyst, and lymphocytic thyroiditis. The majority of these nodules do not need specific treatment once malignancy and abnormal thyroid function are excluded [1, 4, 14, 34].

If patient reports local symptoms including dysphagia, choking, dysphonia, dyspnea, or pain, surgical treatment may be warranted. The clinician should make sure that the symptoms are caused by the thyroid mass or enlargement, and not due to other processes such pulmonary, cardiac, esophageal disorders [4]. Patients with a single toxic nodule or a toxic multinodular goiter may be treated with surgery or radioiodine. Treatment with <sup>131</sup>I for large toxic nodules is not preferred as usually these nodules require high doses and are associated with more side effects [15].

As the rate of growth of benign thyroid lesions is usually slow, observation usually is the plan of

care. FNA-benign thyroid nodules will require long-term follow-up, because some may increase in size and there is always the fear of false-negative FNAs, reported at 1–5 % [35]. Clinical and ultrasound follow-up should be performed at 6–18 months, and periodically thereafter [4, 5].

The need for repeating FNA is a matter of debate. The American Thyroid Association recommends that if the nodule size is stable (no more than a 50 % change in volume or <20 % increase in at least two nodules dimensions in solid nodules or in the solid portion of mixed cystic-solid nodules) the interval before the next follow-up clinical examination or ultrasound may be extended [14]. The American Association of Clinical Endo-crinologists has a very similar approach [15].

Routine use of T4 suppressive therapy in the nodular thyroid disease is not recommended [14, 15]. In young patients with small nodules, colloid features on cytology, and living in iodine-deficient geographic areas, or those with nodular goiters and no evidence of functional autonomy, levothyroxine or iodine supplementation may be considered [36, 37]. Therapy with levothyroxine may be associated with increased risk of atrial fibrillation, other cardiac abnormalities, and reduced bone density, so the therapy should be avoided in patients with large nodules, long-standing goiters, low TSH levels, postmenopausal women, and men older than 60 years [38–40].

## Malignant Thyroid Nodule

If cytologic results are positive for primary thyroid malignancy then surgery is almost always indicated [14, 15]. Metastatic disease to the thyroid needs further investigation to find the primary lesion and usually this precludes immediate surgery. Full workup should also be performed for anaplastic carcinoma and lymphoma [15]. If FNA suggests papillary thyroid cancer a near-total or total thyroidectomy is the procedure of choice, usually including removal of the lymph nodes within the central compartment (level 6), except in cases of intrathyroidal papillary microcarcinoma with no evidence of nodal involvement [3, 14, 15]. In patients with solitary, small (<1 cm) nodule without lymph node involvement proved to be PTC (preoperative or by frozen section) lobectomy plus isthmectomy may be sufficient [14, 15]. Consultation with an experienced endocrine surgeon is preferred and should be done as soon as possible.

## Indeterminate Thyroid Nodule

This group carries the most challenging diagnostic dilemma. In this category a clear cytologic diagnosis cannot be made. Some examples include follicular neoplasms, Hürthle cell neoplasm, atypical PTC, or lymphoma. Nowadays the most acceptable approach is to perform diagnostic surgery to establish a histopathological diagnosis but only 10–40 % of these cases will be malignant, leading to unnecessary surgery with additional costs and risks [41].

Patients with cytology results suspicious for papillary thyroid carcinoma should undergo to surgery as the risk of malignancy is more than 60 % [15, 42]. On the final pathologic analysis most of these lesions will indeed be papillary thyroid carcinoma [28].

Follicular neoplasm, Hürthle cell neoplasm can be found in 15–30 % of FNA cases and carry up to 30 % malignant risk. Atypia or follicular lesion of undetermined significance usually has a lower risk of malignancy, around 5–10 % (Table 4.4) [14, 28, 43]. Repeat biopsy of these nodules is not recommended as can

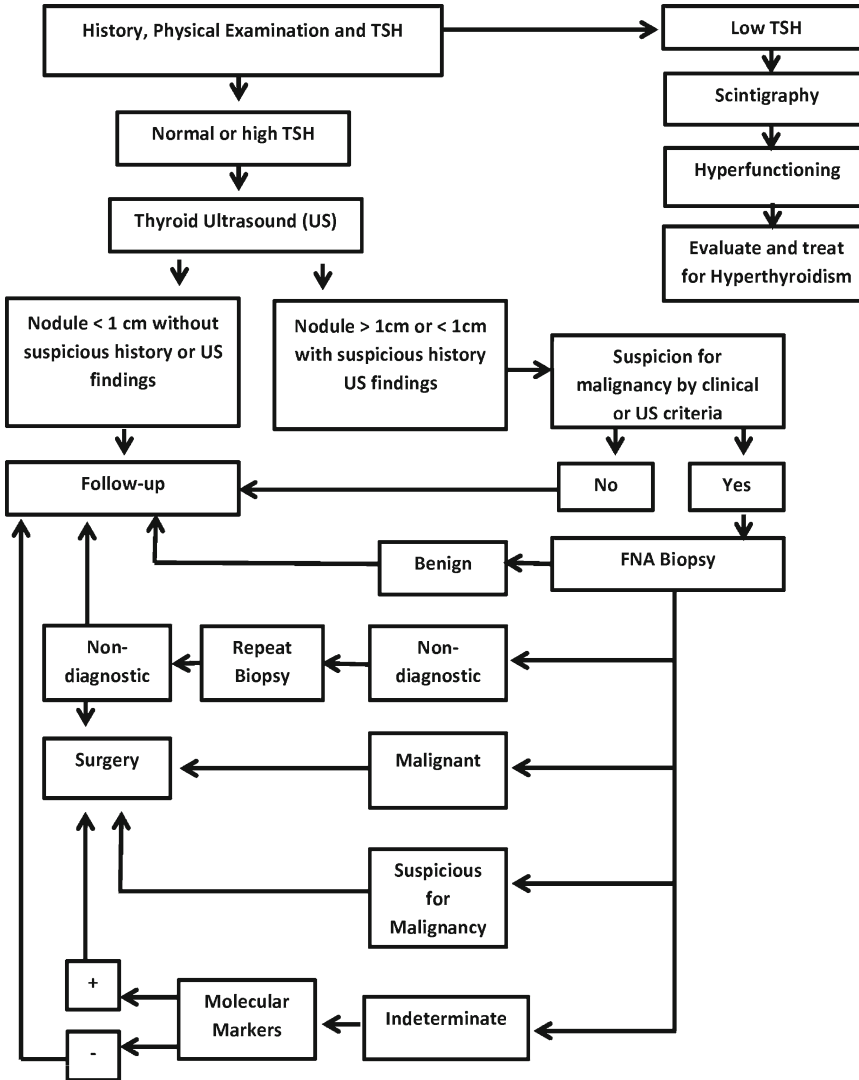
create confusion and often will not provide any additional useful information [15]. Certain clinical features such as male sex, nodules larger than 5 cm, older patient, presence of atypia can improved the diagnostic accuracy for malignancy but overall the predictive values are still low [44–46].

Most physicians when the diagnosis is in question will lean toward surgical intervention. In recent years several molecular and immunohistochemical markers have become available to improve the accuracy of cytologic diagnosis [14, 15, 47]. In practice, the majority of the thyroid nodules do not contain these mutations so surgery is not avoided. Recently, a published study showed that a new gene-expression test may identify low-risk thyroid nodules in indeterminate aspirates but even though with this approach 5–10 % of the nodules classified as benign (false negative) will be malignant, particularly on the group suspicious for malignancy [48]. The key question is to know if these new tests will be able to reduce unnecessary surgeries. If these new tests are able to reduce surgery for indeterminate cytology nodules by one third even with the additional cost of the test we may be able to reduce the overall expenses substantially [49].

Current guidelines describe these tests as expensive and still restricted. There is still lack of evidence and the use of routine use of these markers in clinical practice is still not recommended [15]. Most of the time surgical excision of these lesions is recommended. The initial step usually is a thyroid lobectomy and isthmectomy followed by completion of thyroidectomy depending of the histopathological result.

## Non-diagnostic

Patients with nondiagnostic biopsies are those that do not meet specified criteria (the presence of at least six follicular cell groups, each containing 10–15 cells derived from at least two aspirates of a nodule) [28]. If initial FNA biopsy is nondiagnostic it should be repeated [15]. Most persistently nondiagnostic solid nodules should be surgically excised. A repeat FNA



**Fig. 4.1** Modified Algorithm scheme for the diagnosis and management of palpable thyroid nodules

after initial nondiagnostic cytology may yield a 75 % diagnostic cytologic in solid nodules and 50 % in cystic nodules [50].

Figure 4.1 shows an algorithm with a summary for the diagnosis and management of palpable thyroid nodules.

### Thyroid Cancer

The most common histologic types of thyroid cancer include follicular cell-derived cancers and medullary thyroid lesions.

### Follicular Cell-Derived Cancer

These cancers include the well-differentiated variants of papillary thyroid cancer (vast majority, 85 % of malignant thyroid lesions) and the follicular thyroid cancers (10–15 % lesions), including Hürthle cell cancer. The remaining follicular cell-derived cancer is anaplastic carcinoma that accounts for less than 5 % of the thyroid cancers [51].

Almost the totality of patients with differentiated papillary or follicular cancers will undergo a total or near total thyroidectomy.

Various different classifications and stages exist for risk assessment and evaluation of recurrence and disease mortality. This includes the TNM classification and its stages, MACIS, AGES, and AMES score [52, 53].

This risk assessment evaluation will dictate the follow-up care. Patients will need to be seen regularly ideally by endocrinologist and the most common tests will include TSH, free thyroxine, thyroglobulin tumor markers and thyroglobulin antibodies, thyroid ultrasound, and whole body scan. Treatment includes levothyroxine suppressive therapy and in select cases radioactive iodine ablation therapy [54].

## Medullary Thyroid Cancer

This type of cancer originates in the C cells and accounts for less than 5 % of thyroid malignancies. While the majority has sporadic MTC, around 25 % of patients may have a hereditary form as part of the multiple endocrine neoplasia type 2 syndromes (MEN 2). They will also require thyroidectomy and are followed with tumor markers like calcitonin. Even though the majority of medullary thyroid cancer is sporadic genetic testing is recommended to all patients for evaluation including RET proto-oncogene mutation. If a mutation is found, all family members should undergo screening for the same mutation as early as possible.

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## Special Situations

### Thyroid Nodule During Pregnancy

The majority of the thyroid nodules during pregnancy are preexisting but in some cases they can be initially diagnosed. Overall they should be managed exactly the same way in nonpregnant women except that radioactive agents should be avoided [15, 55]. If the clinical and imaging features are suspicious for malignancy patient will require a FNA biopsy, regardless of the gestational age [14, 56]. Some studies showed that the cancer behavior during pregnancy is the same

when compared to the general population, without any differences in survival rates or recurrence. Suppressive therapy with levothyroxine for thyroid nodules is not recommended.

Patient's preferences should always be considered and a multidisciplinary approach including an endocrinologist, pathologist, obstetrician, surgeon, and anesthesiologist is recommended. Women with no evidence of aggressive thyroid cancer may be reassured and surgical treatment can be performed after delivery [57]. The cytologic suspicious nodule is the most challenge situation during pregnancy. The malignancy rate is similar between pregnant women and nonpregnant women so deferring surgical treatment to the postpartum is reasonable [58]. Some may recommend postponing FNA until delivery unless worrisome features are seen in the ultrasound as this may lead to possible thyroidectomy during pregnancy depending of the FNA results. If the outcome of the results will be unchanged, meaning that surgical treatment will be postponed, this will just expose the patient to anxiety regarding diagnosis and except management [59].

## Thyroid Nodules in Children

The prevalence of thyroid nodules in children is up to 1.8 % and some cohort studies showed higher malignancy rates [60, 61]. These findings suggest that the surgical approach for thyroid nodules in children is more common than adults. The evaluation of nodular disease in children is similar to adults. Overall the prognosis of thyroid cancer in children remains good despite the increase prevalence of local metastatic disease [62]. As in adults, the most common thyroid cancer is the papillary.

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## Summary

Thyroids nodules are very common and usually are benign; around 5 % carry the risk of malignancy. The challenge in the management of thyroid nodules is to correct identify benign nodules and diagnose malignant thyroid disease as early as possible.



Thyroid evaluation starts with a careful history and physical exam followed by thyroid function tests and ultrasound exam. A low TSH requires additional tests for evaluation of hyperthyroidism. When TSH is normal and US shows a suspicious or large nodule a US-FNA should be performed, as it is the single most important procedure for differentiating benign from malignant thyroid nodules. When cytology is suspicious for malignancy surgery is usually recommended. Benign thyroid nodules can be followed clinically and with serial ultrasound images. An indeterminate nodule poses a challenge situation and treatment may include observation, molecular markers or surgery. The most recent revised guidelines come from the American Association of Clinical Endocrinologists and American Thyroid Association, published in 2010 and 2009, respectively [14, 15].

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## Key Points to the Diagnosis

### Radiologic Findings

Pituitary pathology can be identified by abnormalities on plain X-rays, computed tomography (CT), and magnetic resonance imaging (MRI). Enlargement of the bony sella turcica, erosion of the clinoid processes, and intra- or supra-sellar calcifications are findings of pituitary lesions on skull X-ray. Cross-sectional imaging defines the size of the mass, degree of parasellar extension, relationship with other intracranial structures and provides imaging characteristics that suggest the etiology of the lesion. MRI scanning is superior to CT scanning in defining sellar masses and should be obtained in all patients if possible [5]. Clinical decisions regarding further evaluation and management depends on findings that are most accurately demonstrated by MRI imaging (Table 5.1).

Pituitary adenomas are arbitrarily categorized by size as microadenomas (<10 mm) or macroadenomas ( $\geq 10$  mm). On high-resolution CT, pituitary adenomas are typically hypodense compared with the normal gland on both unenhanced and contrast-enhanced images. On MRI imaging [6]

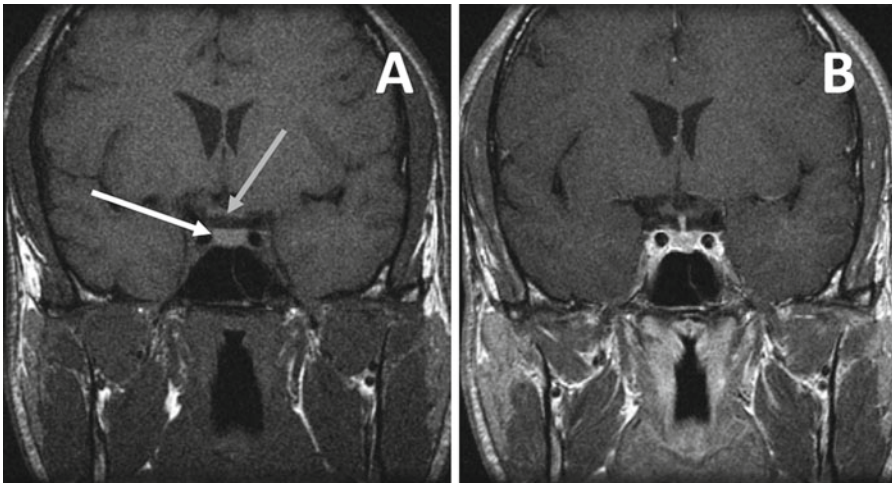
80–90 % of microadenomas appear as a focal hypointense lesion compared with the normal gland (Fig. 5.1) on unenhanced T1-weighted images. After gadolinium, an adenoma typically enhances less avidly than the rest of the gland (Fig. 5.2a). On T2-weighted images up to 50 % of microadenomas are hyperintense. Other findings that can be seen with pituitary adenomas are focal erosion of the sella floor or focal convexity of the superior surface of the gland. Deviation of the pituitary stalk can be seen with microadenomas but may simply represent normal variation. Macroadenomas have similar signal characteristics as microadenomas. Comparing the pre and post contrast signal to the normal pituitary may not be possible as the normal pituitary may be compressed and totally obscured by the macroadenoma. Macroadenomas may grow and extend outside of the confines of the sella turcica. Superior extension of the tumor can cause displacement or compression of the optic nerves and chiasm (Fig. 5.2b). Some adenomas may grow inferiorly, erode through the floor of the sella and fill the sphenoid sinus. Adenomas that invade laterally into the cavernous sinus are unlikely to be cured surgically. Unfortunately both CT and MRI are not highly accurate in predicting cavernous sinus invasion. Encasement of the internal carotid artery is conclusive evidence. A tumor extending beyond the lateral aspect of the internal carotid artery on coronal MRI images is highly suggestive of cavernous sinus involvement. There are cystic variants of pituitary adenomas and cystic degeneration and hemorrhage may also be present.

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**Table 5.1** Sellar, parasellar, and pituitary stalk lesions

Neoplastic	Cysts	Inflammatory/infiltrative	Vascular
Pituitary adenoma	Rathke's cleft cyst	Lymphocytic hypophysitis	Carotid aneurysm
Craniopharyngioma	Arachnoid cyst	Granulomatous hypophysitis	
Chordoma		Sarcoidosis	
Metastasis		Langerhans cell histiocytosis	
Meningioma		Eosinophilic infiltration (Churg–Strauss)	
Germ cell tumor		Infection: bacterial, mycobacterial, fungal, protozoal	
Glioma			
Granular cell tumor (pituicytoma)			
Hypothalamic neuronal hamartoma			
Dermoid			
Pituitary carcinoma			



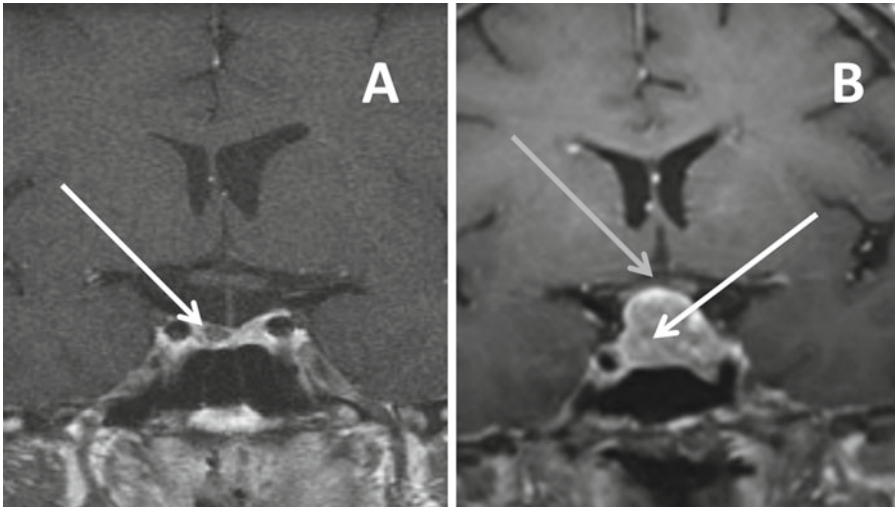
**Fig. 5.1** Normal pituitary gland on MRI T-1 weighted image in the coronal plane prior to contrast (**a**) showing the normal pituitary gland (*white arrow*) and the relation-

ship to the optic chiasm (*gray arrow*). T-1 weighted image after gadolinium (**b**) demonstrates uniform enhancement of the normal pituitary gland and infundibulum

The imaging characteristics of Rathke's cleft cysts [6] reflect their etiology. These non-neoplastic cysts arise from remnants of epithelium from Rathke's pouch. They are typically seen in the center of the gland, although they can be laterally located or present in the suprasellar space (Fig. 5.3). Many of these cysts are isointense with cerebral spinal fluid (CSF) on MRI imaging, however, if they contain proteinaceous fluid they may be hyperintense on T1- and T2-weighted sequences. They lack contrast enhancement and do not contain calcifications. Occasionally a Rathke's cleft cyst can enlarge and compress the optic chiasm.

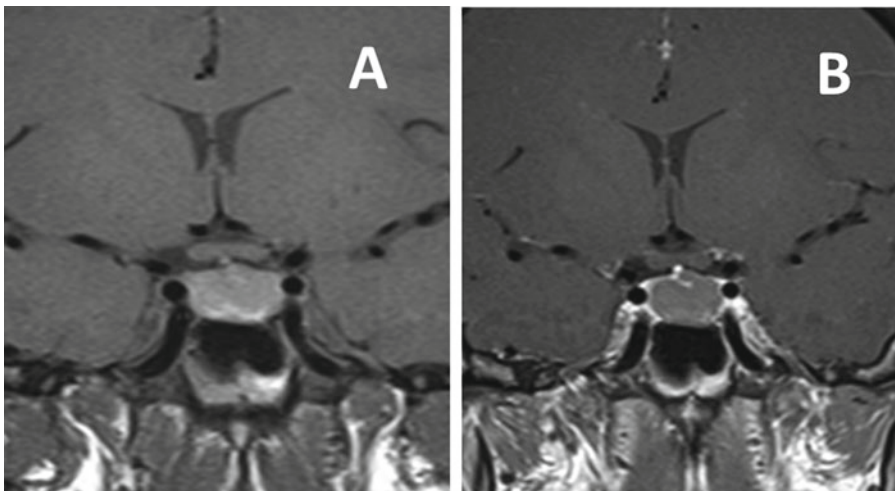
### History, Physical Examination, and Laboratory Findings

Symptoms, findings on physical examination and laboratory abnormalities associated with pituitary tumors are due to the effects of hormonal excess, hormonal deficiency or local effects the mass on surrounding tissues. Detailed questioning regarding the symptoms, and examination for the physical signs associated with excess and deficiency of each hormonal axis should be obtained. Symptoms related to mass effect include vision loss which is classically loss of peripheral vision from compression of



**Fig. 5.2** MRI T-1 weighted images in the coronal plane after gadolinium showing: (a) a pituitary microadenoma (*white arrow*) located in the right side of the gland that enhances

less than the normal pituitary tissue and (b) a pituitary macroadenoma (*white arrow*) with suprasellar extension displacing and deforming the optic chiasm (*gray arrow*)



**Fig. 5.3** MRI T-1 weighted images in the coronal plane showing an intrasellar Rathke's cleft cyst. Prior to contrast (a) the cyst shows mild increased intensity compared to normal brain. After gadolinium (b) the cyst does not enhance

the optic chiasm. Other patterns of visual loss can occur due to anatomic variation in the anatomy of the optic nerves and chiasm. As vision loss can occur very slowly over years some patients may not be aware of vision loss even in the presence of significant visual field deficits. Although loss of peripheral vision may be demonstrable on physical examination, automated perimetry should be obtained with masses

that approach or contact the optic apparatus. Headaches are unlikely to occur with small masses that are confined to the sella. Larger masses with extrasellar extension can cause headaches. Interestingly, likely due to slow growth and tissue adaptation, many patients with huge sellar based masses do not have headaches. The sudden onset of a severe headache, acute onset of symptoms of pituitary insufficiency and

cranial nerve deficiency such as diplopia or ptosis can be seen with hemorrhage in a pituitary adenoma (pituitary apoplexy). Polyuria and polydipsia will be present in lesions affecting the posterior pituitary, pituitary stalk or hypothalamus that cause deficiency of antidiuretic hormone (diabetes insipidus). Although it is uncommon, many different systemic illnesses can involve the pituitary and parasellar area and a thorough review of systems should be completed. If the history or physical exam suggests hormonal excess or deficiency the appropriate hormonal laboratory evaluation should be obtained including dynamic testing if necessary. The laboratory evaluation for asymptomatic patients with a pituitary mass is discussed below.

### **Evaluation of the Incidentally Found Pituitary Mass**

Clinicians are commonly presented with patients who have had a pituitary mass incidentally discovered. The “pituitary incidentaloma” is defined as an asymptomatic mass in the pituitary, found on imaging done for an unrelated reason. The majority of these lesions are small, usually less than 1 cm in diameter, and represents either pituitary adenomas or Rathke’s cleft cysts. To decide what tests, if any, should be obtained and if treatment or observation is indicated, one needs to confirm the patient is asymptomatic and also consider the potential for, and the clinical impact of, hormone deficiency, hormone excess, and tumor growth.

Incidentally found macroadenomas are commonly associated with hormone deficiencies with a reported prevalence of hypopituitarism ranging between 15 and 57 % [7, 8]. The presence of hormone deficiencies in incidentally found microadenomas is controversial, likely reflecting the arbitrary size cutoff of greater or less than 1 cm. and the fact that subtle deficiencies may be present despite normal baseline hormonal levels. Retrospective studies suggest that incidentally found microadenomas have a very low chance of being associated with hormonal hypofunction with most studies reporting a 0 % incidence.

However, this needs to be interpreted in light of a study [9] involving 38 patients with microadenomas (55 % incidentally found, 45 % found on imaging done to evaluate abnormal laboratory tests suggesting pituitary dysfunction). GH releasing hormone (GHRH)/arginine stimulation found 50 % of these patients to be GH deficient. In addition, basal hormone levels and/or 1 µg Cortrosyn stimulation identified at least one deficiency of gonadotropins, TSH, and/or ACTH in 50 % of the patients. This led the Endocrine Society task force that developed the clinical guidelines for pituitary incidentalomas to favor screening for hormone deficiency in tumors greater than 5 mm [5].

Recommendations vary widely as to the specific laboratory tests that should be obtained. Given the current literature, laboratory testing to identify subclinical hypopituitarism in asymptomatic patients with an incidentally found pituitary mass should be obtained when the mass is greater than 5 mm in size (Table 5.2). It is reasonable to obtain TSH and free thyroxine to rule out secondary hypothyroidism, IGF-1 to screen for GH deficiency, and a morning cortisol level to screen for secondary adrenal insufficiency, realizing that basal levels of IGF-1 and morning cortisol may not be adequate to determine normalcy or deficiency and dynamic testing may be required. Obtaining a testosterone level in men and a menstrual history in women will determine if hypogonadism is present. Measuring LH and FSH may be helpful in some instances, for example if there is concern about coincidental primary hypogonadism.

The most common hormone overproduced in incidentally found pituitary masses is PRL with an incidence of 12–28 % [8, 10, 11]. Prolactin measurement should be done after serial dilutions of the serum in macroadenomas as falsely low values may be present when prolactin concentration is in fact very high due to the high dose hook effect of the assay [12]. Prolactinomas have potential for morbidity, testing is easy, and safe and effective treatment is available.

The incidence of GH overproduction by an incidentally found mass is between 2 and 8 % [8]. In early cases symptoms and physical findings

**Table 5.2** Recommended hormonal tests for asymptomatic patients with an incidentally found pituitary mass

	To rule out subclinical hormone excess	To rule out subclinical hormone deficiency	
		Size $\leq 5$ mm	Size $> 5$ mm
Prolactin <sup>a</sup>	X		
IGF-1 <sup>b</sup>	X		X
FT4, TSH			X
Testosterone (men)			X
Menstrual history (premenopausal women)			X
AM Cortisol <sup>b</sup>			X

<sup>a</sup>Measure after dilutions in macroadenomas to rule out high dose hook effect

<sup>b</sup>IGF-1 and AM cortisol levels may not be sufficient to indicate normalcy or deficiency and dynamic studies may be necessary

may be quite subtle, but there is potential for serious morbidity and mortality if GH excess is not detected. There is also a high likelihood of surgical cure when the tumor is small.

No instances of ACTH excess have been reported in clinical studies of pituitary incidentaloma. Autopsy studies report between 1 and 13.8 % of the adenomas stained for ACTH [13]. The screening tests for ACTH excess are cumbersome to perform and, particularly in asymptomatic patients, have high false positive rates [14]. Although Cushing's disease is serious, screening for ACTH excess in patients with no clinical suspicion of glucocorticoid excess is not recommended due to the low prevalence and the high false positive rate of the screening tests [5].

Although autopsy studies indicate 4 % of incidentally found adenomas stain for gonadotropins, LH and FSH are usually in the normal range and are often biologically inactive in surgically proven gonadotropin adenomas. Rare cases of elevated testosterone levels in men and ovarian hyperstimulation in women due to gonadotropin secreting pituitary adenomas have been reported [15, 16]. If a clinical syndrome is present with a gonadotropin producing adenoma it is usually hypogonadism associated with a macroadenoma.

TSH secreting pituitary adenomas are exceedingly rare, and none have been reported in clinical or autopsy series of incidentally found masses. These usually present clinically as macroadenomas with symptoms of hyperthyroidism [17]. Routine screening in the setting of a pituitary incidentaloma is not recommended.

Given the frequency and the clinical impact of over production of the various hormones, and the sensitivity and specificity of the screening tests, it is reasonable to obtain levels of PRL and IGF-1 to rule out subclinical excess secretion for all truly asymptomatic patients with incidentally found pituitary masses (Table 5.2).

An automated visual field examination should also be obtained at baseline if a macroadenoma is approaching or contacting the optic chiasm on MRI images [5]. This serves to determine if there is subclinical vision loss and also to serve as a baseline to determine if future growth, or surgical or radiation treatment, caused new vision loss.

Both microadenomas and macroadenomas have the potential to increase in size over time. Growth may occur after several years of stability. Macroadenomas likely grow more often (7–51 %) than microadenomas (0–14 %) [3]. Any increase in size of a macroadenoma has a higher chance of causing clinically significant mass effects.

Observation is appropriate if there is no hormonal over or under production, and the mass is not causing or threatening vision loss. If the decision is made to observe, repeat imaging with MRI scanning should be done initially at 6–12 months, and then annually for 2–4 years, and periodically thereafter. Doubling the interval since the last scan if no change is noted is appropriate. With macroadenomas, follow-up should include hormonal assessment for hypopituitarism, assessment for symptoms of mass effect and imaging with MRI. Since the decision to do surgery on a nonfunctioning macroadenoma is going to rest primarily on the development of vision loss, formal visual fields (if the mass is in proximity to the optic chiasm) should be obtained at these same intervals. All follow-up scans should be compared to the baseline scan in addition to the prior scan, since minor consecutive increases in size may not be appreciated.



## Differential Diagnosis

A wide spectrum of lesions with various etiologies can manifest as masses in the sellar or parasellar region (Table 5.1). Excluding pituitary adenomas and Rathke's cleft cysts, they represent only about 6 % of clinically apparent lesions [4]. Brief discussions of some of these lesions follow.

Craniopharyngiomas are tumors of epithelial origin that can affect both children and adults. Craniopharyngiomas are often located in the suprasellar space but can be within the sella. They can appear solid on imaging but often contain both solid and cystic components. Calcifications, seen on plain X-ray or CT, may be present. These tumors commonly present with vision loss, anterior pituitary hormone deficiencies, and diabetes insipidus [18].

Chordoma is an aggressive, rare bone cancer that is locally invasive, and has a predilection for the axial skeleton, with the most common sites being the sacrum, skull base, and spine. Parasellar chordomas usually involve the dorsum sella, clivus, or nasopharynx and cause local bone destruction (best seen on CT). Symptoms of headache or neck pain are common and diplopia or facial numbness can occur if cavernous sinus invasion is present [19].

Germ cell tumors can affect the central nervous system. The pineal gland is the most common site for intracranial germ cell tumors. These tumors can also be located in the suprasellar region, basal ganglia, posterior fossa, pituitary gland, or medulla. They may manifest as multiple discrete lesions and leptomeningeal spread occurs in 10–15 % of cases. Common symptoms include headache, diplopia, hypopituitarism, and diabetes insipidus [20]. They typically present in teenagers or young adults (peak incidence age 10–14 years) and rarely present in patients greater than 30 years old. The diagnosis can be facilitated by measuring the tumor markers beta-human chorionic gonadotropin ( $\beta$ HCG) and alpha-fetoprotein (AFP), which may be present in blood or CSF.

Metastatic tumors to the sellar area are usually asymptomatic from the pituitary standpoint and typically are found in patients with known

metastatic disease. The posterior lobe of the pituitary or the hypothalamus are more commonly involved making diabetes insipidus the most common pituitary related symptom. Metastases may also cause anterior pituitary dysfunction, vision loss, diplopia, and retro-orbital pain. The most common primary sites are breast, lung, gastrointestinal tract, kidney, prostate, and melanoma [21].

Primary brain tumors may present in or around the sella. Parasellar meningiomas are often located by dorsum sella or clivus [22]. Radiologically meningiomas are typically isointense to hypointense to gray matter on T1-weighted MRI sequences and isointense to hyperintense on T2-weighted MRI sequences. They typically display intense homogeneous enhancement and may show calcification. Gliomas located in the parasellar region often arise from the optic nerves or optic chiasm and have an unpredictable clinical course [23].

Lymphocytic hypophysitis is a presumed autoimmune inflammation of the pituitary which is more common in premenopausal women (80–90 %), often presenting during pregnancy or postpartum, but can occur in men, children, and the elderly [24]. Recently it has been reported as a side effect of ipilimumab, an anticancer monoclonal antibody that stimulates cytotoxic T-lymphocytes [25]. Symptoms commonly include headache which is often intense. Pituitary insufficiency may involve only one hormone axis, including diabetes insipidus, or multiple hormone deficiencies may be present. Imaging can be variable showing diffuse pituitary enlargement, enlargement of both the pituitary and pituitary stalk, stalk enlargement only which may appear as a suprasellar mass. Usually homogeneous contrast enhancement is present. Occasionally a presumptive diagnosis of lymphocytic hypophysitis is made with a normal appearance of the pituitary on imaging.

Neurosarcoidosis can affect the parasellar region and often involves the hypothalamus and/or pituitary stalk [26]. Angiotensin converting enzyme (ACE) levels usually are elevated in the blood or CSF. Other organs are typically affected at some point in the course of the disease, but parasellar neurosarcoidosis can be the only manifestation.

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## Present and Future Therapies

### Transsphenoidal Surgery

Since the 1970s, the standard surgical approach for most pituitary tumors has been via the sublabial transsphenoidal route [27]. This approach to the sphenoid sinus involves making a sublabial incision for access to the nasal cavity and then removing the nasal septum. The sphenoid sinus is then entered allowing access to the sella turcica. After resection of the tumor the nasal septum is replaced requiring nasal packing postoperatively. In the mid-1990s, surgeons began using a modification of the standard surgical technique utilizing the nasal endoscope [28]. With this endoscopic transnasal transsphenoidal approach, there is no external incision. The nasal endoscope is placed through one nostril and advanced to the anterior wall of the sphenoid sinus. The sphenoid ostium is identified and enlarged and the posterior portion of the vomer is removed allowing access to the sphenoid sinus. After placement of a self-retaining nasal speculum, the sella turcica is entered and the neurosurgical portion of the procedure is undertaken as with the sublabial transseptal approach. After resection of the tumor the nasal speculum is withdrawn, the nasal septum adjusted to midline if necessary, and a mustache nasal dressing is applied. The main difference in the two procedures from the surgeon's standpoint is that with the endoscopic transnasal approach the surgical field is smaller and is angled approximately 10° off-center [29]. The disadvantages this may present to the surgeon can be overcome with experience [30].

For the patient, the absence of the sublabial incision eliminates the possibility of developing lip numbness postoperatively and leaving the nasal septum intact decreases postoperative discomfort from nasal packs and decreases the chance for complications related to the nasal septum. Additionally, the length of hospitalization, anesthesia time and blood loss are reportedly less with the endoscopic approach [31, 32].

Operative success regarding extent of tumor resection, normalization of visual deficits, and normalization of hormonal hypersecretion are

similar or better using the transnasal endoscopic technique. Surgical complications, including mortality, vision loss, new pituitary hormonal deficits, CSF leak, and infection are comparable between the two procedures [29, 33–39].

### Radiation

Radiation therapy of pituitary adenomas has been used as primary therapy for pituitary adenomas as well as for treatment of residual or recurrent tumors after surgery. The major limiting factor for radiation therapy is damage to the normal surrounding tissues. For pituitary adenomas the radiation must pass through normal brain tissue and the tumors are often adjacent to radiation sensitive structures such as the optic nerves and normal pituitary gland.

The state of the art for fractionated X-ray radiotherapy is termed fractionated stereotactic radiation therapy (FRST) and is an improvement over conventional radiation therapy (CRT) in that it uses techniques to increase the radiation dose to the tumor while limiting the exposure of normal tissues. Control of non-functioning pituitary adenoma growth appears to be better with FRST compared to CRT [40].

Stereotactic radiosurgery is a technique using multiple lower dose X-ray radiation beams conformationally focused on the tumor and delivered in a single session. It has proven to be effective with both non-functioning and hormone-secreting pituitary adenomas for patients with recurrent or residual tumors after surgery or if medical therapy has failed. Inhibition of further tumor growth occurs in greater than 95 % of patients treated with radiosurgery for non-functioning adenomas [41].

Patients with hormone-secreting pituitary adenomas treated with radiosurgery have a very wide range of reported biochemical remission, varying from 17 to 82 % [42]. This variation in published reports on remission rates following radiosurgery for hormone-producing pituitary adenomas likely is due to advances in the technique over time, varied definitions of endocrine cure, and relatively short follow-up periods after radiosurgery.

It remains controversial whether pituitary-suppressive medications (somatostatin analogues or dopamine agonists) at the time of radiosurgery have any impact on remission of hormone hypersecretion. Several studies have noted that patients using either somatostatin or dopamine agonists at the time of radiosurgery for GH- or PRL-secreting tumors less frequently achieved biochemical remission [43, 44]. A study of 46 acromegalic patients who underwent radiosurgery found that patients who did not receive pituitary-suppressive medications at the time of radiosurgery were four times more likely to reach normal GH and IGF-1 levels than those who had [42]. Conversely, some studies have failed to find any association between biochemical remission rates for acromegalic patients who received somatostatin analogues at the time of radiosurgery and those who did not [45, 46].

The primary adverse effect of pituitary radiosurgery is the development of new anterior pituitary hormone deficits. The development of new pituitary hormone deficits ranges between 7 and 41 % in studies with mean follow-up intervals of 4–5 years. The different rates of hypopituitarism reported likely relate to variation in the patient characteristics including history of prior surgery or fractionated radiation therapy, radiation dose prescribed, treatment volume, follow-up intervals, and the completeness of the patients' endocrine evaluation [47].

An alternative to X-ray radiation is using proton therapy as the radiation source. Proton therapy exposes normal tissue closer to the surface of the body to lower radiation doses than the tumor receives and is effective in treating functioning and non-functioning pituitary adenomas [48]. Due to the high cost of developing a proton therapy center its availability is limited to 41 centers worldwide as of 2012 [49].

## Medical Therapy

Medical therapy is used to decrease hormone overproduction by functioning pituitary adenomas or block the effects of excess hormone secretion, and in some instances may be used to

decrease tumor size relieving symptoms of mass effect or to limit further growth.

For patients with prolactinomas, medical treatment with a dopamine agonist is usually the first line therapy. Cabergoline and bromocriptine are the agents most commonly used and both are effective in normalizing PRL secretion and decreasing tumor size with cabergoline being more efficacious and more tolerable than bromocriptine [50]. Some patients achieve prolonged remission after 2 or more years of treatment. Cardiac valve disease has been described with cabergoline therapy but is rare in patients treated with the standard doses used for the treatment of hyperprolactinemia. Patients, especially those on doses of cabergoline greater than 2.0 mg/week should be periodically assessed for valvular heart disease. Impulse control disorders can occur in patients treated with dopamine agonists for Parkinson's disease and restless legs syndrome and has also been reported in patients with prolactinomas [51].

GH secreting pituitary adenomas are usually initially treated with surgery and/or radiation therapy. Medical therapy is used with persistent disease after surgery, while waiting for the effects of radiation, and occasionally as primary therapy in selected patients unable to tolerate surgery or with clearly unresectable disease [52]. The somatostatin analogues octreotide and lanreotide, given by intramuscular or subcutaneous injection, respectively, act by decreasing GH secretion from the adenoma. Normalization of IGF-1 levels occurs in approximately 60 % of patients. Tumor size can decrease in some patients, but the decrease is modest and usually not clinically significant. Common side effects include nausea and diarrhea but these usually resolve despite continued therapy. Development of gallstones occurs in up to 30 % of patients but rarely is symptomatic requiring therapy. In patients with mild GH excess, treatment with the dopamine agonist cabergoline may normalize IGF-1 secretion. Pegvisomant, a GH receptor antagonist, normalizes IGF-1 levels in 90 % of patients, is usually well tolerated but can cause drug induced hepatitis. Increase in the size of the adenoma has been reported in some patients.

Historically, the only medical therapies for patients with ACTH producing pituitary adenomas and persistent cortisol excess after transphenoidal surgery or radiation were drugs that suppressed adrenal cortisol production (e.g., ketoconazole, metyrapone) by inhibiting steroidogenic enzymes [53]. Their efficacy however decreases with time as the continued ACTH stimulation overrides the enzymatic block. Because of this, their role is primarily in correcting severe hypercortisolism in the short term prior to definitive surgical treatment. Hepatotoxicity can occur with ketoconazole requiring monitoring of hepatic enzymes. Emerging medical therapies include pasireotide and mifepristone. Pasireotide, a new somatostatin analog, has high binding affinity for four of the five known somatostatin receptor subtypes (sst<sub>1-3</sub> and sst<sub>5</sub>). ACTH producing adenomas can express multiple sst receptors, with the predominant receptor being sst<sub>5</sub>. Octreotide and lanreotide which are not effective in treating ACTH producing adenomas, have high affinity for sst<sub>2</sub> and low affinity for sst<sub>5</sub>. Pasireotide, with a 40-fold higher affinity for sst<sub>5</sub> than octreotide, normalized or decreased by  $\geq 50\%$  urinary free cortisol in approximately 50% of treated patients after 6 months. Hyperglycemia related adverse events however occurred in 73% of patients with 46% requiring initiation of, or an additional glucose lowering medication [54]. Mifepristone, a cortisol receptor antagonist has been shown to improve glycemic parameters, lower diastolic BP, and improve clinical signs and symptoms in patients with Cushing's syndrome from various etiologies [55]. Adverse events however occurred in 88% of the subjects. As cortisol levels rise during treatment, hormonal levels cannot be used to monitor treatment, and overtreatment resulting in adrenal insufficiency may be difficult to detect.

Laparoscopic bilateral adrenalectomy is an established, safe, and effective treatment for patients with persistent Cushing's disease after pituitary surgery. Cortisol excess is immediately and definitively cured, but lifelong hormonal replacement with glucocorticoids and mineralocorticoids is required. There is potential for unrestrained growth of a residual ACTH producing pituitary adenoma after adrenalectomy (Nelson–Salassa syndrome). The vast majority of patients

do not require tumor-directed therapy after adrenalectomy as Nelson–Salassa syndrome typically occurs in the small subset with a clear evidence of invasive pituitary disease at the outset [56]. There are no studies comparing clinical outcomes of bilateral adrenalectomy versus medical therapy for patients with persistent disease after pituitary surgery.

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## Pathophysiology

PRL is secreted by the lactotrophs present in the anterior pituitary gland and its secretion is under the inhibitory control of hypothalamic dopamine that reaches the anterior pituitary gland through the portal circulation via the pituitary stalk. Sellar and suprasellar tumors as well as inflammatory and infectious diseases evolving pituitary stalk prevent the inflow of the dopamine to lactotrophs, leading to increased PRL secretion. Moreover, there are several factors releasing PRL secretion, as estrogen, serotonin, thyrotropin-stimulating hormone (TRH), and vasoactive intestinal peptide (VIP) [1].

Hyperprolactinemia, defined by elevated serum PRL levels above the normal range, is the most common hypothalamic-pituitary dysfunction and can result from several causes, as physiological conditions (pregnancy, breastfeeding, stress); pharmacological and pathological status, like kidney and liver failure, hypothyroidism, pituitary adenomas, tumors or other inflammatory diseases of the hypothalamic-pituitary region, and macroprolactinemia. Prolactinomas,

adenomas with autonomous secretion of PRL, are the most common pituitary tumors, with a prevalence of 100 cases per million, more often reaching young women, being ten times more frequent in females aged 20–50 years-old than in males. Nevertheless, the prevalence becomes similar between genders in adults over 60 years-old [1]. The differential diagnosis of hyperprolactinemia is essential for its proper treatment.

Secretion and pulsatility of gonadotropin-releasing hormone (GnRH) is impaired in hyperprolactinemia, leading to gonadotropin deficiency and consequent hypogonadism. The classic manifestations, in both sexes, are: sexual dysfunction, infertility, menstrual irregularities, and bone mass loss [1]. Galactorrhea, often found among women with hyperprolactinemia, is not a mandatory or specific sign. Batrinos et al. evaluated 404 women with galactorrhea, with and without irregular menses and the prevalence of hyperprolactinemia was 42 and 15 %, respectively [3]. Mass effects as headache and visual disturbances are often found [1] in macroprolactinomas and other tumors of the hypothalamic-pituitary region.

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## Key Points for Diagnosis

Hyperprolactinemia is defined when serum PRL levels are above the normal reference value (20–25 ng/ml in females, 15–20 ng/ml in males) [4]. The stress of venipuncture can increase PRL secretion, frequently at levels slightly above the normal value. When blood collection is performed

after rest, about 30 % of asymptomatic individuals with mild hyperprolactinemia present with normal hormonal levels [5]. Nevertheless, rest for blood withdrawal is not routinely recommended.

Serum PRL evaluation should be performed only when clinically indicated [1].

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## Differential Diagnosis

After confirming the diagnosis of hyperprolactinemia, the following etiologies should be evaluated [6]:

- Physiological: pregnancy and lactation, mammary stimulation
- Pharmacologic: neuroleptic and antipsychotic medications (sulpiride, chlorpromazine, risperidone, haloperidol), antidepressants, opioids, cocaine, antihypertensive medications (verapamil, methyl dopa), drugs that act in the gastrointestinal tract (metoclopramide, domperidone), protease inhibitors for AIDS treatment, and the use of estrogens
- Associated with systemic diseases: kidney and liver failure
- Associated with endocrinological diseases: primary hypothyroidism, polycystic ovarian disease (PSOD), Addison's and Cushing's diseases
- Other tumors of the hypothalamic-pituitary region or infectious/infiltrative disorders compromising the pituitary stalk [7], as pituitary nonfunctioning macroadenomas, craniopharyngiomas, metastasis, lymphocytic hypophysitis, sarcoidosis, tuberculosis; in addition post-surgery or radiotherapy status can also lead to hyperprolactinemia
- Intercostals' nerves stimulation
- Autonomous PRL secretion by pituitary adenomas: prolactinomas, mixed PRL and GH secretion tumors
- Macroprolactinemia
- Idiopathic

In pharmacological hyperprolactinemia, a new serum PRL evaluation should be performed after 3 days of withdraw of the suspected drug, if possible. Otherwise, the patient should undergo magnetic resonance imaging (MRI) of the pituitary to rule out pathological causes [8].

In primary hypothyroidism, increasing PRL secretion is attributed to TRH and serum PRL levels should decrease and become normal after appropriate levotiroxine replacement [9].

Regarding polycystic ovarian disease (PSOD), more recent studies did not confirmed any pathophysiological relationship with hyperprolactinemia and the coexistence of these two conditions could just be a random association [10]. Therefore, in patients who remain with irregular menses after reaching normal serum PRL levels, it is important to exclude other causes for the symptoms, such as PSOD.

Mammary stimulation in nonpregnant women, as chest wall disturbances (herpes zoster, mechanical or chemical trauma) can lead to increased levels of PRL due to neurogenic reflex [11]. Breast clinical examination, mammography and ultrasound have minimal effect on serum PRL levels [12].

Macroprolactinemia is characterized by the predominance of the PRL isoform big-big-PRL (macroprolactin), which occurs in about 25 % of hyperprolactinemic individuals. According to its molecular weight, PRL is classified as monomeric, dimeric and macroprolactin. Monomeric PRL corresponds to more than 50 % of total circulating PRL and it is considered the biological active isoform, while macroprolactin has low biological activity [13]. In an individual with macroprolactinemia and normal serum concentrations of monomeric PRL, symptoms related to hyperprolactinemia are not expected [14, 15]. Macroprolactinemia is an important cause of dissociation between clinical and laboratory findings and its screening should be performed in asymptomatic hyperprolactinemic individuals in which the request for the initial PRL evaluation is debatable. However, symptomatic hyperprolactinemia can occur in macroprolactinemia patients when monomeric isoform is also elevated [15].

Dealing with a patient with symptomatic hyperprolactinemia, pregnancy, use of medications that may cause hyperprolactinemia, kidney failure, liver failure, and hypothyroidism are excluded, sellar MRI should be performed in order to identify a pituitary tumor with autonomous PRL secretion (prolactinoma) or other tumors of the sellar region, as well as infiltrative or infectious diseases, are the cause of hyperprolactinemia by pituitary



stalk disconnection. Serum PRL is usually proportional to the tumor size in prolactinomas: in microprolactinomas, serum PRL levels until 200 ng/ml are expected while in macroprolactinomas frequently values above these levels are found [16]. Karavitaki et al. [17] evaluated serum PRL levels in patients with pituitary nonfunctioning tumors with pituitary stalk disconnection and in 98.7 % of the cases, levels were lower than 95 ng/ml. Therefore, in hyperprolactinemia due to disconnection, serum PRL does not exceed 100 ng/ml, with few exceptions. The differentiation between a hyperprolactinemia due to disconnection and prolactinomas is essential, especially in the presence of mass effect, in order to indicate proper therapy.

When all the above mentioned causes were ruled out and sellar MRI is normal, diagnosis of idiopathic hyperprolactinemia is made, albeit the presence of microadenomas not detectable in the image cannot be excluded [6].

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## Current Therapies and Future Perspectives

Treatment goals include eugonadism restoration status and galactorrhea resolution. In the presence of macroadenoma, treatment also aims to control its growth and preserve, or even restore pituitary function, when this is impaired. The therapeutic modalities available for prolactinomas are: medical, surgical, irradiation, and their associations.

## Medical Treatment

Dopamine agonists (DA) are the gold standard for the treatment of prolactinomas being most represented by bromocriptine (BRC) and cabergoline (CAB). This class of drugs promotes PRL gene transcription inhibition, PRL secretion decrease, as well as reduction of prolactinoma dimensions [1]. CAB became the drug of choice due to its better tolerance and efficacy, explained by the high affinity and specificity to dopamine receptor subtype 2 [1]. The initial dose of CAB is usually one tablet of 0.5 mg twice per week, and the titration is carried out according to the decrease of PRL levels and tumor dimensions

[18]. The use of CAB leads to normal serum PRL levels in over 85 % of cases and tumor reduction by more than 80 % of them, while BRC promotes normal serum PRL levels in 80 % and reduction of tumor dimensions in 70 % of cases [19].

The most common DA side effects are nausea, vomiting, and postural hypotension, and rarely nasal congestion, cramps and psychiatric disorders [20]. CAB was related to valvulopathy in patients with Parkinson's disease, in whom very high doses of CAB are used and there is a higher prevalence of other risk factors for heart valve disease. CAB, not BRC, has an agonist activity at serotonin receptor 5HT2B, which can promote fibroblast proliferation and valvular insufficiency, especially in tricuspid and pulmonary valves. However, valvulopathy due to CAB treatment for hyperprolactinemia is still controversial. Amongst 16 studies published about this issue [21–31], only one showed an association between CAB's use and the presence of moderate tricuspid insufficiency [23]. Moreover, in other four [22, 25, 28, 31] there was a higher prevalence of valvular regurgitation, especially in the tricuspid valve, without clinical repercussion. In two studies, valve structure changes were described, with a greater risk of fibrosis [30] and calcification [31] compared to the control group. Nonetheless, in our opinion individualized monitoring with echocardiography is desirable until more consistent data will be available. Recent data pointed to remission of hyperprolactinemia after withdrawal of the drug in substantial number of patients. Passos et al. [32] obtained normoprolactinemia after BRC withdrawal in 20.6 % of patients (25.8 % in microprolactinomas and 15.9 % in macroprolactinomas) after drug use for a median time of 44 months. Even higher remission ratios were observed by Colao et al. [33] using with CAB for a median time of 40 months (69 % in microprolactinomas and 64 % in macroprolactinomas). Dekkers et al. [34], in a recent meta-analysis of 19 studies about DA withdraw, showed that the mean number of patients in remission was 21 % with a higher nonsignificant tendency toward CAB (35 %) compared to BRC (20 %). Although the guideline of Endocrine Society [18] suggests that DA suspension should be performed gradually, in patients treated for at least 2 years, we suggest that the removal of DA should be individualized.

In patients with drug related hyperprolactinemia when drug cannot be discontinued and in patients with idiopathic hyperprolactinemia or microprolactinomas without desire of fertility (particularly with resistance or intolerance to DA), use of hormone replacement can be indicated [18].

## Surgical Treatment

Considered secondary in the therapeutic algorithm of prolactinomas, the indications for surgery include: DA resistance/persistent intolerance, absence of visual impairment reversal in a short period of DA use; symptomatic apoplexy; cerebrospinal fluid leakage and/or visual compromise due to tumor shrinkage with chiasma retraction with DA treatment. Surgery is usually performed through microscopic or endoscopic transsphenoidal route and their results depend on neurosurgeon's experience and skillness, on serum PRL levels, and on tumor's size and the invasiveness. Gillam et al. [35] reviewing 50 surgical series showed remission in 74.7 % of microprolactinomas and in 33.9 % of macroprolactinomas. The recurrence rate in this same analysis was 18.2 and 22.8 %, for microprolactinomas and macroprolactinomas respectively.

## Radiotherapy

Prolactinomas are amongst the most radioresistant pituitary adenomas, and therefore radiotherapy is limited to aggressive tumors resistant to usual treatments. Gillam et al. [35] reviewing published data show that the normalization average of PRL levels were similar with radiotherapy utilizing conventional technique (34.1 %) and stereotactic (31.4 %) with radiation therapy. Side effects include damage to the optic tract; 50 % risk of hypopituitarism in 10–20 years, neuropsychological disturbances, the development of secondary tumors, and stroke.

## Fertility and Pregnancy

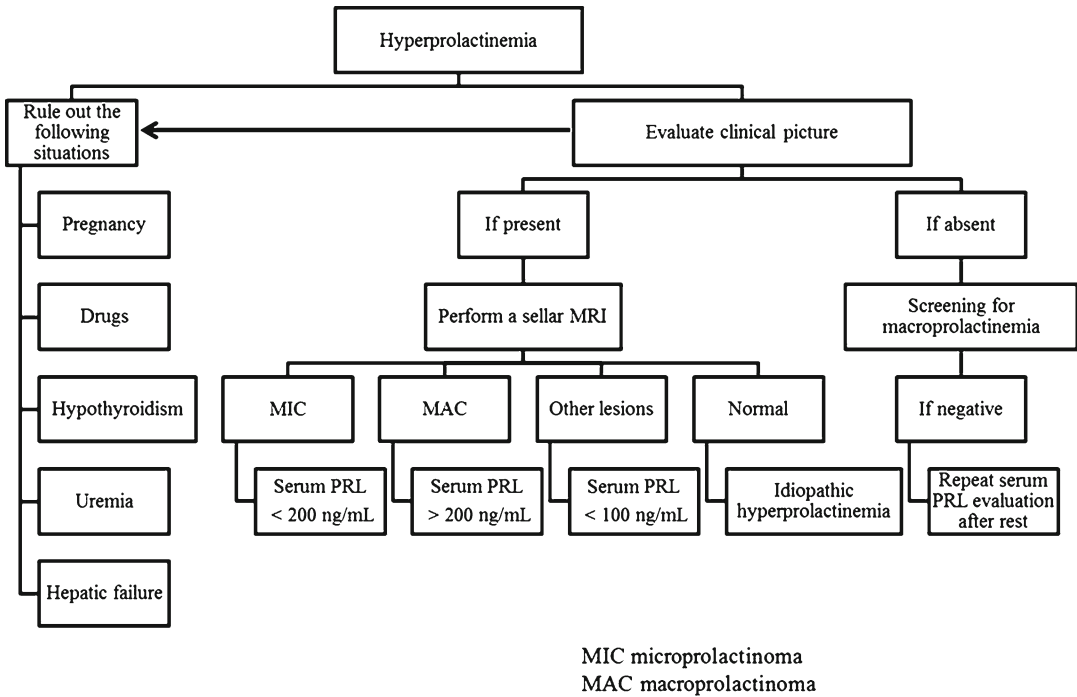
Treatment with DA restores fertility in most cases. In the absence of response to drug treatment, and in cases of microprolactinomas or

intrassellar macroprolactinomas, ovulation induction with clomiphene citrate or recombinant gonadotropins may be used [36].

The risk of tumor growth with clinical consequences during pregnancy is up to 5 % in microprolactinomas, and therefore, upon confirmation of pregnancy, DA should be withdrawn. Clinical follow-up should be done in each pregnancy trimester, not being indicated a systematic assay of PRL. In the presence of significant headache or visual complaints confirmed by a neuroophthalmologic evaluation, sellar MRI without contrast is indicated, preferably after the first trimester. If a significant tumor growth is detected, DA should be reintroduced. In patients with macroadenomas, however, the risk of clinical significant tumor growth with is higher: 15–35 %. Therefore, in patients with expansive macroprolactinomas, we must wait for the tumor reduction to the sellar boundaries for at least 1 year of treatment with DA, before allowing pregnancy. When the tumor does not shrink, surgical treatment is indicated. The maintenance of DA throughout pregnancy is up to the specialist discretion. Neuroophthalmological evaluation should be performed periodically. Reintroduction of the drug is indicated when tumor growth occurs. If this is not effective, surgical treatment should be performed preferably in the second trimester [37]. In men, in addition to sexual dysfunction, hypogonadism in hyperprolactinemia can promote changes in sperm quality, mainly astenospermia [38]. In men with prolactinoma on DA with persistent hypogonadism, with or without normalization of serum PRL, the use of clomiphene citrate has been proven useful in the recovery of the gonadotropic axis. This approach has advantages over testosterone replacement by restoring fertility [39].

## Addressing Prolactinomas Resistant and/or Aggressive

Aggressive pituitary tumors are defined by the presence of extensive expansion or invasiveness of neighboring structures, rapid tumor growth or recurrence, or the presence of giant tumor, with more than 4 cm in diameter. Diagnosis of



**Fig. 6.1** Diagnosis of hyperprolactinemia algorithm

pituitary carcinoma is performed only in the presence of metastases. They are extremely rare, being PRL secretion tumors the most prevalent. Aggressive prolactinomas are more common in young male patients. The prevalence of prolactinomas resistant to DA is approximately 10 % of microprolactinomas and 18 % of macroprolactinomas [1]. Reduction of dopaminergic D2 receptors is its principal mechanism [40].

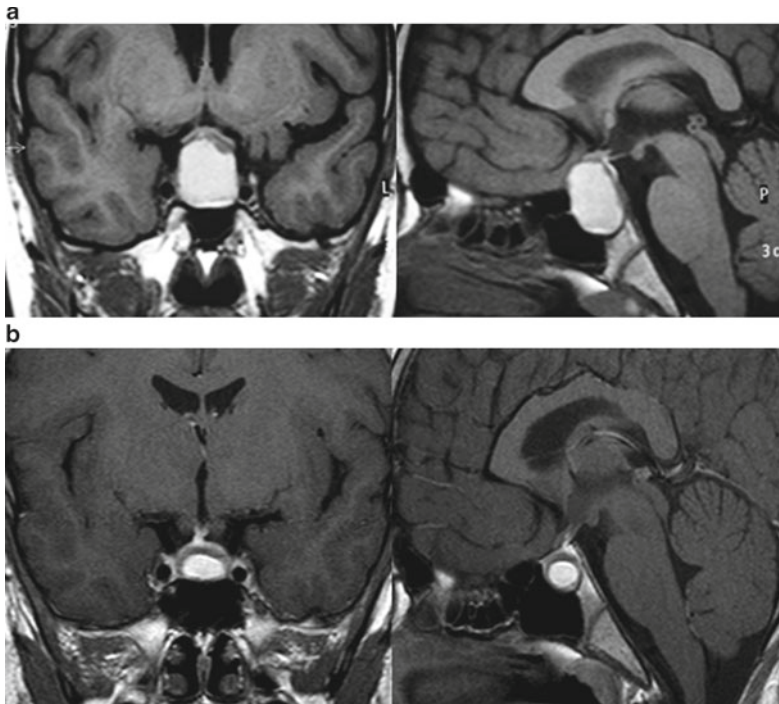
The initial strategy to treat patients partially resistant to DA is the stepwise increase dose. Ono et al. [24] achieved normalization of PRL levels in 96.2 % of patients with dose up to 12 mg per week of CAB, an exceeding elevated dose. Other strategies, most of them still undergoing clinical trials, are the use of somatostatin analogs targeting different somatostatin receptor subtypes, the use of estrogen receptor modulators, PRL receptor antagonists, antiproliferative drugs such as the alkylating agent temozolomide, and mTOR or tyrosine kinase inhibitors.

Surgical treatment, even non-curative, may be effective in obtaining normoprolactinemia in patients partially resistant to DA [41, 42].

## Summary: Diagnosis and Treatment

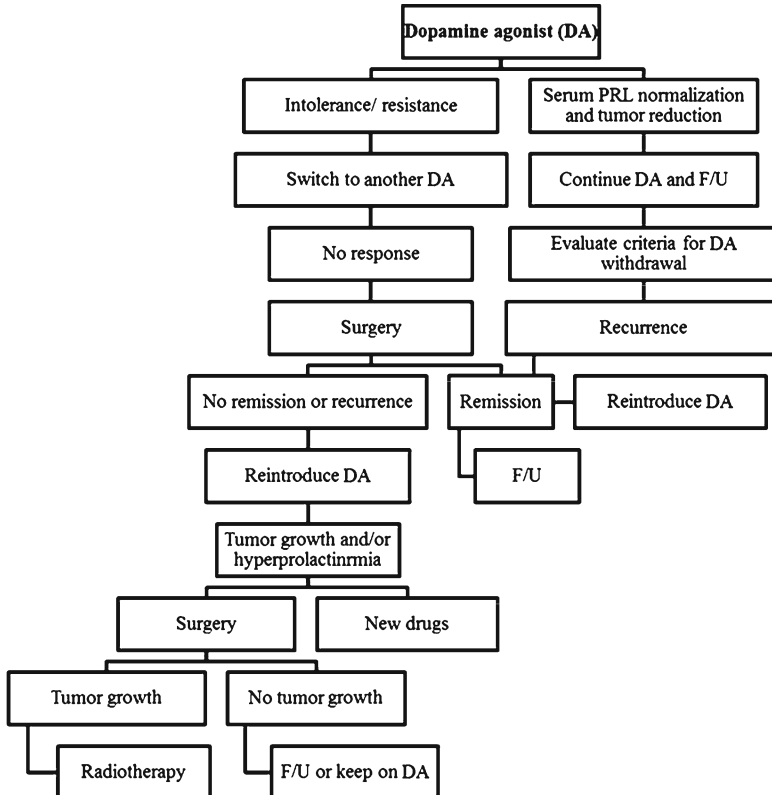
Hyperprolactinemia is a major cause of hypogonadism and infertility, especially among young women. Diagnosing the cause of this condition is essential for appropriate treatment indication. Figure 6.1 summarizes the steps for diagnosis in an algorithm. In idiopathic hyperprolactinemia and prolactinomas, the treatment of choice is the use of DA. Surgical treatment and radiation are options for cases of resistance or intolerance to DA. Figure 6.2 depicted sellar MRI of a patient with macroprolactinoma in whom surgery was indicated. The algorithm suggested for the treatment is in Fig. 6.3.

A sellar MRI was performed in a 11-year-old male patient complaining of headache and a sellar mass was depicted (Fig. 6.2a). Serum PRL level was 1,130 ng/ml. The patient also had pubertal impairment development. Neuroophthalmologic evaluation was normal. After 4 years of treatment with BRC, there was tumoral reduction without normalization of serum PRL levels. In our department, BRC was



**Fig. 6.2** (a) Before treatment. Sellar T1-weighted MRI after gadolinium enhancement, coronal (*left*) and sagittal (*right*) depicted a sellar mass impinging optic chiasma. (b) After 1 year of treatment with CAB. Sellar

T1-weighted MRI after gadolinium enhancement, coronal (*left*) and sagittal (*right*) depicted an important reduction of tumor dimensions, with optic chiasma free of compression



**Fig. 6.3** Prolactinoma treatment algorithm

substituted for CAB and dosage was gradually augmented until 3.5 mg a week. After 1 year of treatment with CAB, serum PRL levels were normal and an additional tumoral reduction occurred (Fig. 6.2b).

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### The Regulation of Growth Hormone Secretion

The somatotrophs of the anterior pituitary secrete growth hormone in pulses, predominantly at night, in response to regulation by the hypothalamic peptides Growth Hormone-Releasing Hormone (GHRH) and somatostatin. GHRH is secreted from neurons in the arcuate nucleus and premammillary area into the portal system [5], with expression also found in the anterior hypothalamus, dorsomedial and ventromedial nuclei [5, 6] to stimulate somatotrophs to both synthesize and secrete GH [7]. Somatostatin is a 14 amino acid peptide that is widely distributed throughout the hypothalamus, and acts on somatotrophs to suppress GH secretion (Fig. 7.1), though another form of somatostatin comprising 28 amino acids also exists [8]. Somatostatin acts via a family of five receptors and somatostatin nerve terminals synapse on the hypothalamic GHRH dendrites and cell bodies in the arcuate nucleus [9] to suppress both basal and GHRH-stimulated GH release, but it does not affect GH synthesis [10].

GH secretion is also regulated by ghrelin, a growth hormone secretagogue-receptor ligand

[11] that is mainly synthesized in the gastrointestinal tract, particularly the stomach, but is also found in the central nervous system. Gastric expression of ghrelin is reduced following feeding and increased by fasting and may play a role in the regulation of GH secretion with eating [12].

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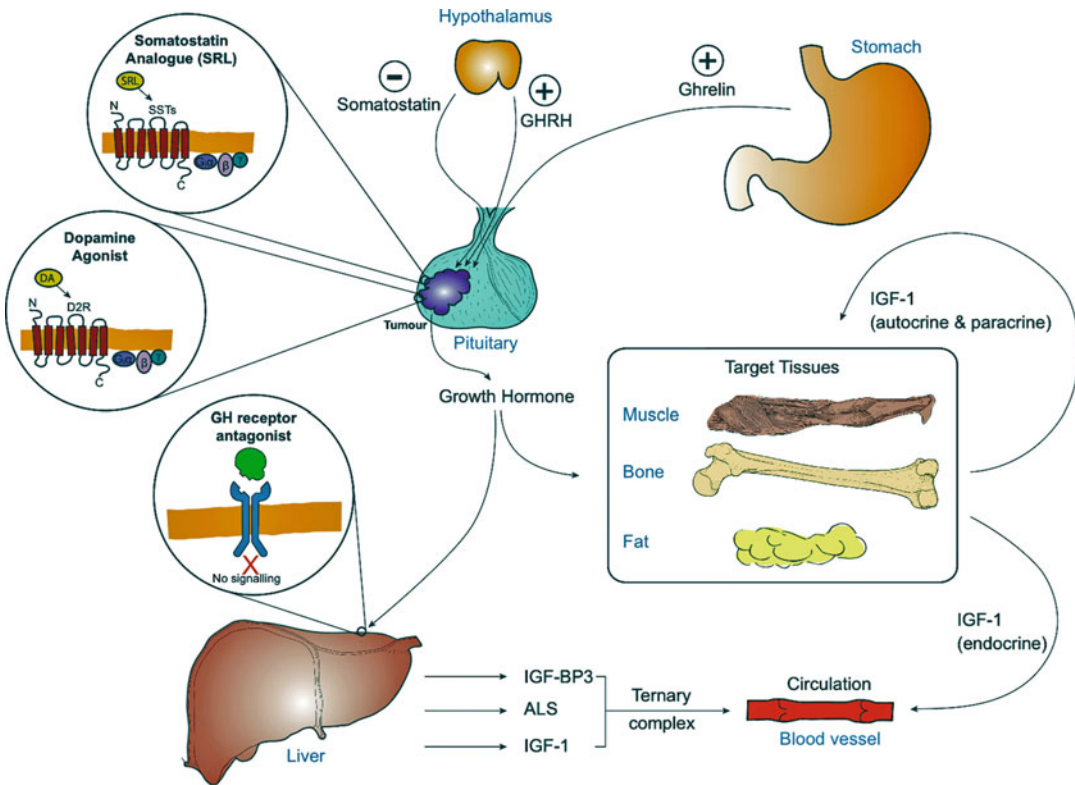
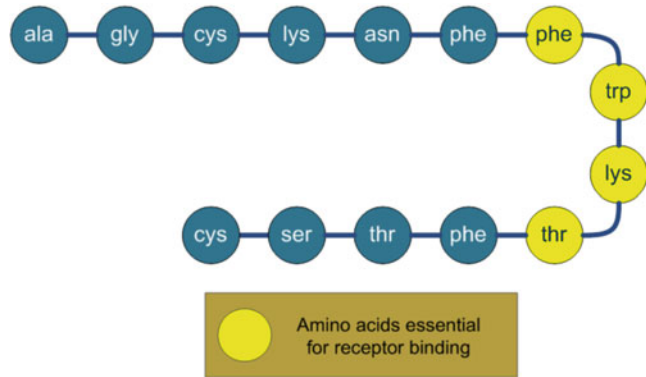
### IGF-I

IGF-I is responsible for most of the growth promoting actions of growth hormone (Fig. 7.2) and exerts a negative feedback on the synthesis and secretion of growth hormone [13, 14]. It is a single chain protein consisting of 70 amino acids cross-linked by three disulfide bridges, with a molecular mass of 7.6 kDa and is encoded by a gene on the long arm of chromosome 12 at position 23.2. IGF-I is secreted by many tissues, including adipose tissue, bone, muscle and kidney, and acts in an endocrine, autocrine and paracrine manner (Fig. 7.2). In mice, knockout of hepatic expression of IGF-I gene reduces circulating IGF-I levels by 80 % but has little impact on linear growth emphasizing the importance of its autocrine and paracrine actions. The A and B domains of IGF-I are homologous to the A and B chains of insulin, but the C domain shares no sequence homology [15]. IGF-I binds to a specific transmembrane tyrosine kinase receptor with activation leading to the phosphorylation of numerous substrates including the insulin receptor substrate family of proteins.

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**Fig. 7.1** Peptide structure of Somatostatin



**Fig. 7.2** The growth hormone-IGF-1 axis in acromegaly secondary to a pituitary tumour, indicating the site of action of the drugs used in the treatment of acromegaly

IGF-I circulates in the plasma bound to a specific family of binding proteins (IGFBPs). These binding proteins act as circulating carriers and transport the IGF-I out of the vascular compartment, deliver IGFs to specific cell types, and modulate IGF binding to receptors and growth-promoting function [16]. The majority of circulating IGF-I

is in a tertiary complex formed from IGF-binding protein 3 (IGFBP3) and acid labile subunit (ALS) [17], which cannot cross the vascular epithelial layer and serves as a reservoir of IGF-I within the circulation (Fig. 7.2). Free IGF-I has a half-life of around 12 min, in contrast to over 12 h for the tertiary complex [17].



Circulating levels of IGF-I are highest in late adolescence and decline during adulthood. The levels are high in pregnancy and lower in patients with liver disease, hypothyroidism and poorly controlled diabetes [18].

## Acromegaly

### Clinical Features

Acromegaly is a condition defined and recognized for its phenotype which reflects the widespread expression of growth hormone receptors (Table 7.1).

#### CNS

Patients may present due to mass effect from a large tumour such as headaches, visual field defects and cranial nerve palsies due to cavernous sinus invasion.

**Table 7.1** Clinical features of acromegaly [18]

<i>CNS</i>	<i>Respiratory</i>
Headache	Sleep apnoea
Visual field defects	Impaired respiratory function
Cranial nerve palsies	
<i>Musculoskeletal</i>	<i>Gastrointestinal</i>
Prognathism	Colonic polyps
Frontal bossing	Colonic malignancy
Maxillary widening	Visceromegaly
Jaw malocclusion	<i>Endocrine and metabolic</i>
Increased soft tissue thickness including	Hyperprolactinemia
Hands and feet	Menstrual abnormalities
Arthritis and arthralgia	Galactorrhoea
Carpal tunnel syndrome	Reduced libido
<i>Skin</i>	<i>Hypopituitarism</i>
Skin tags	Thyroid goitre
Sweating	Insulin resistance
Oily skin	Impaired glucose tolerance
Acanthosis nigricans	Diabetes mellitus
<i>Cardiovascular</i>	<i>Hypertriglyceridemia</i>
Hypertension	Hypercalciuria
Left ventricular hypertrophy	
Cardiomyopathy	
Congestive cardiac failure	
Arrhythmias	

### Musculoskeletal

Soft tissue growth and skeletal enlargement cause changes in the physical appearance that can be subtle and easily missed in the early stages of the disease. Changes in the face include prominence of the forehead and orbital ridges with thickening of the skin leading to frontal bossing, wide and thickened nose, prominent cheekbones, thickening of the lips, macroglossia, mandibular overgrowth with prognathism, maxillary widening, separation of the teeth and malocclusion of the jaw. It is often useful to compare old and current photographs, as the changes are very insidious.

Patients may report an increase in shoe size or ring size. Enlargement of hands results in the so-called “spade-like” appearance and the palms have a typical doughy consistency.

Accelerated degenerative changes in the weight bearing joints like the hips, knees and spine lead to a degenerative arthropathy, with arthralgia being a very common complaint. Large joint arthropathy occurs in 70 % patients secondary to the thickening of periarticular cartilaginous and fibrous tissue. 50 % patients have an axial arthropathy with restriction of movement and joint deformity [1], commonly affecting the lumbar area. Carpal tunnel syndrome occurs in 30–50 % of patients and is often bilateral but up to 80 % patients may show electrophysiological evidence of median neuropathy due to increased oedema of the median nerve in the carpal tunnel, rather than extrinsic compression from an increased volume of carpal tunnel contents [19]. Muscle hypertrophy may be present but the muscles may be weaker [20]. The thorax may be deformed due to protrusion of the lower portion of the sternum and divergence of the ribs [21].

### Skin Changes

Up to 70 % of patients have oily skin with sweating being a very common symptom. The skin is thickened due to glycosaminoglycan deposition. Pigmented skin tags over the trunk are common. Acanthosis nigricans may develop in patients with severe acromegaly.

## Cardiovascular System

Cardiovascular complications are a major cause of mortality in acromegaly with up to 60 % patients dying from cardiovascular disease [22], although there is no evidence of an excess of ischaemic heart disease. Hypertension affects approximately one-third of the patients with acromegaly and is associated with an expanded plasma volume, but the mechanism is ill-understood as there is no evidence that the renin–angiotensin system or catecholamines are involved in the pathogenesis [22, 23]. Kamenicky et al. demonstrated that GH with IGF-1 stimulates epithelial sodium channel mediated sodium transport in the late distal nephron, providing insight into the pathogenesis of sodium retention in acromegaly. Insulin resistance and diabetes possibly play a role in the development of hypertension [24].

Initial cardiac involvement is asymptomatic and concentric cardiac hypertrophy has been known to occur early in the condition [25, 26]. This hypertrophy is followed by a diastolic dysfunction and finally systolic dysfunction [27]. All this can lead to cardiac failure with features of a dilated cardiomyopathy. Arrhythmias are more frequently reported in patients with acromegaly, especially during exercise and these include ectopics, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, bundle branch blocks and ventricular tachycardia [28]. There is also an increased prevalence of valvular disorders in patients with acromegaly [29] and this risk increases with time from onset [30].

## Respiratory System

Respiratory complications contribute to approximately 25 % of mortality seen with acromegaly. The respiratory problems are secondary to changes affecting facial bones and soft tissues, respiratory cartilages, lung volumes, shape of the ribcage and respiratory muscle activity [22]. The two main issues encountered are sleep apnoea and impaired respiratory function. The main cause of sleep apnoea is narrowing of the upper airways causing an obstructive sleep apnoea, although a few patients have a central cause. Impaired respiratory function is due to anatomical

alterations in the chest wall as well as changes in lung elasticity. These patients may also have kyphoscoliosis, which may worsen the respiratory problems.

## Endocrine and Metabolic Features

Hyperprolactinemia is seen in about 30 % of patients due to pituitary stalk compression or co-secretion of GH and prolactin by the tumour [31]. TSH co-secretion with consequent hyperthyroidism is reported. Compression of the normal pituitary tissue by the tumour results in varying degrees of hypopituitarism in approximately 40 % of patients [32]. Menstrual irregularities or erectile dysfunction, decreased libido, secondary hypothyroidism and hypoadrenalism may be seen. Goitre is common, on occasion associated with hyperthyroidism [33].

Insulin resistance and diabetes mellitus occur secondary to the anti-insulin effects of GH [34]. Hypertriglyceridemia secondary to insulin resistance is described but interestingly total cholesterol and LDL-cholesterol levels are lower in active acromegaly and rise with treatment [22, 35]. GH stimulates  $1\alpha$  hydroxylase, which increases the levels of 1,25-dihydroxycholecalciferol resulting in increased intestinal absorption of calcium and urinary calcium loss and potentially hypercalcaemia [36].

Controversy still exists as to the extent of cancer risk in patients with acromegaly. A direct association between acromegaly and cancer is yet to be proven [37, 38]. Gastrointestinal tumours are the most common malignancies, which may reflect that the colon is longer in patients with acromegaly but there is also evidence that [39] recurrent colonic adenomas (but not hyperplastic polyps) showed a correlation with IGF-I levels [40]. In a retrospective cohort study, colon cancer mortality but not incidence was found to be higher [41]. It is recommended that patients who have acromegaly should be offered a screening colonoscopy at baseline [42]. The frequency of repeat colonoscopy should depend on the findings of the original screening and should be according to the international guidelines for colon cancer [42].

## Biochemical Confirmation of Acromegaly

The rarity of the disease means that the greatest challenge in the diagnosis of acromegaly is for the disease to enter the differential diagnosis of the presenting manifestations, and this is reflected in typically a decade lapsing between development of symptoms and confirmation of the diagnosis. Once considered, the diagnosis is usually rapidly confirmed by biochemical testing and imaging.

### Biochemical Tests

An undetectable (<0.3 mcg/l) random GH measurement is good evidence against a diagnosis of acromegaly, but an elevated value is of limited value as it may be a pulse in a healthy individual. For that reason a combination of an oral glucose tolerance test and serum IGF-I measurement are required in suspected acromegaly, with results being unequivocally abnormal in patients with acromegaly.

The gold standard test for a biochemical diagnosis of acromegaly is the 75-g oral glucose tolerance test. Growth hormone level is measured at baseline and at every 30-min intervals for 2 h. In normal individuals, GH levels fall with at least one value being <0.3 mcg/L, with failure of suppression or a paradoxical rise in GH being indicative of acromegaly.

When interpreting GH data, and in particular when applying international consensus criteria to local practice, it must be appreciated that although the performance of GH assays, by some criteria, have improved, that by others their clinical applicability has deteriorated, for example the bias between different commercial assays has increased. In other words, the reported value for a given sample can vary greatly dependent on the assay methodology and it is erroneous to ascribe undue biological significance to a given consensus cut-off such as 0.3 mcg/L, but rather recognize that it is “best-guess” that is assay bias dependent. The origins of assay bias are discussed elsewhere [43].

GH can fail to suppress during an OGTT in patients with uncontrolled diabetes mellitus, liver

or renal disease, patients receiving oestrogen, during pregnancy and late adolescence, malnutrition and anorexia, but in combination with IGF-I measurement and examination of the patients there is rarely a problem [18]. It should not be difficult to distinguish anorexia from acromegaly!

The utility of IGF-I measurement is hindered by concerns over the quality of some commercial assays and their reference ranges. This is a rare problem with the diagnosis of acromegaly as the levels are normally unequivocally elevated—an IGF-I within the reference range in newly diagnosed acromegaly is very rare. A greater problem is apparently elevated IGF-I levels in patients who do not have acromegaly. The explanation of such findings is uncertain and probably lies with limitations of assay design and reference ranges and often results in extensive investigation to disprove the diagnosis. All IGF-I assays must first be thoroughly validated and standardized to the new International IGF-I standard IS02/254. Furthermore, many of the clinical frustrations related to IGF-I assessment are a consequence of the inadequacies of the reference range. Brabant et al. established the gold standard reference range by collecting data for 3,961 healthy subjects [44].

IGF-I levels may vary, typically being low in liver and renal dysfunction and uncontrolled diabetes mellitus. Nutrition, circadian rhythm, oestrogen, insulin, glucocorticoid therapy and thyroxine levels can affect IGF-I levels.

### Imaging

Magnetic resonance imaging (MRI) with gadolinium contrast is the imaging modality of choice and can detect tumours as small as 2 mm; although more than 75 % of patients have a pituitary tumour >10 mm in diameter. When an extrapituitary source of GH or GHRH is suspected, abdominal and chest CT with or without MRI may be needed. In the rare cases of ectopic GHRH the pituitary typically has a hyperplastic appearance.

### Functional Pituitary Testing

As with any pituitary tumour, evidence of hypopituitarism must be sought using standard protocols.

Elevated prolactin levels could be secondary to compression of the pituitary stalk or due to the tumour co-secreting GH and prolactin. Prolactin levels  $>5,000$  mU/L indicates co-secretion; with more minor degrees of hyperprolactinaemia the aetiology is less certain. Elevated GH levels suppress hepatic cortisol binding globulin (CBG) expression and lower the circulating CBG levels. Therefore in active acromegaly measurement of total serum cortisol may underestimate free cortisol and after successful surgery apparent recovery in circulating cortisol can be seen, which is actually a consequence of an increase in CBG.

Visual field testing should be undertaken in all patients with macroadenomas.

### Morbidity, Mortality and Defining Disease Control

The excess mortality of acromegaly [45] is multifactorial in origin with important contributors being cardiomyopathy, hypertension, hyperglycaemia or diabetes and sleep apnoea.

There is accumulating evidence that vigorous treatment and good biochemical control (see below) not only reduces morbidity but also restores life expectancy to normal [45–50].

GH values and IGF-I should be used as complementary tests to assess for disease control and activity. It is not uncommon to get a discrepancy between the GH and IGF-I levels [51], most commonly with normal GH levels and an elevated IGF-I although the reverse can be seen. Factors that can lead to discrepancies include prior radiotherapy, and gender. Women have lower IGF-I levels for a given GH level than men, an effect exaggerated by the use of oral oestrogen [52]. GH levels fall rapidly after surgery but IGF-I can take in excess of 3 months to reach its nadir.

### Remission Criteria

The definition of disease control has become more rigorous over the past decade. This is partially due to the recognition that mortality associated with

**Table 7.2** Acromegaly treatment outcomes [53]

Outcome	Criteria	Management
Active acromegaly	Random GH $>1$ $\mu\text{g/L}$ and nadir GH after OGTT $\geq 0.4$ $\mu\text{g/L}$	Frequent MRI
	Elevated IGF-1	Monitor and actively treat comorbidities
	Clinical features of active disease	Actively treat or consider change of treatment
Controlled acromegaly	Random GH $<1$ $\mu\text{g/L}$ or nadir GH after OGTT $<0.4$ $\mu\text{g/L}$	Periodic but less frequent MRI
	Age–sex normalized IGF-1	No change to treatment, consider reducing SSA dose

acromegaly reduces with an improvement in the biochemistry.

Optimal disease control is currently defined as a random GH level of  $<1$   $\mu\text{g/L}$  using an ultrasensitive assay or nadir GH of  $<0.4$   $\mu\text{g/L}$  on OGTT; and an IGF-I in the age-adjusted normal range [52] (Table 7.2). When there is discrepancy between GH and IGF-I values, multiple GH sampling (three to five times over 2 h) is suggested. For patients on medical treatment with a somatostatin receptor analogue or dopamine agonist, IGF-I and random GH measurements may suffice [52]. An OGTT is not helpful for monitoring response in patients receiving medical treatment. Patients on treatment with a growth hormone receptor antagonist are monitored using IGF-I levels only.

### Management

Advances in pituitary surgery, the development of new pharmaceutical interventions and refinements in radiotherapy mean that tumour control and biochemical remission can be achieved in the overwhelming majority of patients. The challenge is optimizing the treatment algorithm recognizing local variations in access to the treatment modalities and ensuring minimal treatment related morbidity.

## Surgery

The transsphenoidal microsurgical approach is the appropriate initial treatment in the great majority of patients. In expert hands, approximately 80 % and 50 % of patients with micro- and macroadenomas, respectively, achieve normal IGF-I levels [53, 54]. While the merits of endoscopic approach with or without intra-operative MRI are debated, unquestionably the choice of the surgeon is crucial, illustrated by the variation in published outcomes between centres in the UK [55]. Cure rates as low as 17.8 % have been reported in one centre in which multiple neurosurgeons were undertaking a small number of cases each [56], which improved to 67 % with a restructuring of the service to one dedicated pituitary surgeon [57]. There is also a plethora of evidence of morbidity and mortality being lower in the hands of specialist pituitary surgeons [58].

Complications of pituitary surgery include diabetes insipidus, which is usually transient. CSF rhinorrhoea and rarely meningitis may occur. Alteration in the sense of smell, epistaxis and sinusitis may be seen. The syndrome of inappropriate ADH secretion (SIADH) with hyponatremia may be seen transiently in the post-operative period. It is typically seen 7 days following surgery and usually resolves with fluid restriction. The main long-term complication is hypopituitarism, which may be seen in 10–20 % cases [59] depending on tumour size and the surgeon's experience. Damage to the optic nerve or to the carotid artery should be seen very rarely (<1 %) and mortality should be less than 0.5 %.

## Radiotherapy

Pituitary radiotherapy is very effective at controlling tumour growth and, with time, controls GH secretion and normalizes IGF-I. Conventional multi-fractionated, 3-field radiotherapy delivering 4,500 cGy has fallen out of favour, particularly in younger people, because of the risk of cerebrovascular accidents but still has a place in the treatment of patients with large and growing residual tumour after surgery. GH values can be

anticipated to reduce by up to 50 % in the first 2 years, followed thereafter by a continuing slow decline [60]. IGF-I normalization is also seen in 60 % patients after 10 years, so somatostatin analogue therapy is often required for many years post-irradiation. Hypopituitarism is the most common complication. In one large series, 10 years after irradiation, 27 % developed TSH deficiency, 18 % developed FSH/LH deficiency and 15 % developed corticotropin deficiency [60].

Stereotactic high dose pituitary irradiation has in many centres supplanted conventional radiotherapy most frequently being delivered by the Gamma Knife®. These techniques require precise delineation of the tumour to ensure there is minimal surrounding tissue exposure and therefore are more suitable for smaller volumes residual tumour beyond the reach of the surgeon.

Among case series of GH adenomas treated with radiosurgery, tumour control was attained in 97 % cases with hormonal remission rates varying from 17 to 96 % [59]. Hypopituitarism is the most common side effect.

## Medical Treatment

### Dopamine Receptor Agonists

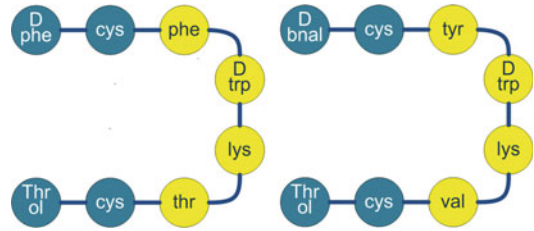
Dopamine receptor agonists, acting through the D2 receptor (Fig. 7.2), were the first effective medical therapy for acromegaly and continue to have a place in its treatment, often in combination with somatostatin analogues, particularly as they have the twin virtues of being relatively inexpensive and orally administered. Early studies with bromocriptine documented suppression of GH levels to <5 µg/L in about 15 % patients when used in high doses of up to 20 mg/day with corresponding reductions in symptoms like soft tissue swelling and headache [61]. Cabergoline is a long-acting ergot-derived dopamine agonist that has superseded bromocriptine as it is more potent and better tolerated. Doses of up to 1 mg/day normalize IGF-I in up to 30 % patients [62]. Cabergoline is probably most effective in patients with prolactin co-secretion when it is likely to also induce some tumour shrinkage [63]. Cabergoline is not licensed for the treatment of acromegaly and dose finding and large scale prospective studies have not been undertaken so it is

probable that the potential of cabergoline has not been fully exploited either in terms of biochemical control or tumour shrinkage. Side-effects include gastrointestinal discomfort, nausea, vomiting, dizziness, headache and postural hypotension but in most patients these are manageable by slow dose titration. The more concerning side effects include induction of depression or mania often in patients with a prior history or very rarely development of gambling, alcohol and sex addiction in patients with no history of previous psychiatric problems. There is evidence in patients with Parkinson's disease, of ergot-derived dopamine agonists causing cardiac valve fibrosis with the risk being related to cumulative dose [64] and although the doses used in endocrine patients are much smaller and there is a dearth of evidence of a problem in patients with pituitary adenomas, annual echocardiograms are recommended.

### Somatostatin Analogues (SSAs)

Somatostatin is a regulatory peptide produced by neuroendocrine, inflammatory and immune cells in response to specific stimuli and it acts on numerous tissues including the pituitary gland to inhibit GH secretion. The various actions of somatostatin are mediated by five subtypes of receptors (SST1-5) [65]. Somatostatin cannot be used for therapy of acromegaly as it has a very short plasma half-life (2–3 min) and lacks specificity as it binds all five receptor subtypes. Octreotide and lanreotide are somatostatin analogues with prolonged plasma half-lives and high affinity for the SST2 and SST5 receptors responsible for the regulation of GH secretion from somatotrophs [18]. Figure 7.3 shows the structures of octreotide and lanreotide.

Somatostatin analogues are the treatment of choice for most patients not cured by surgery. Prospective clinical trials indicate that biochemical disease control is achieved in 60–70 % of patients with the results being better in patients with milder disease [18]. Experience captured in the British observational registry of patients with acromegaly suggests a “real-life” normalization rate in an unselected patient population of nearer 50 %. Even when biochemical control is sub-optimal, the great majority of patients experience



**Fig. 7.3** Structure of octreotide and lanreotide

biochemical and symptomatic benefit from octreotide and lanreotide. In such patients the addition of cabergoline may result in a further fall in GH and IGF-I levels accompanied by relief of symptoms [66].

In the last decade there has been increasing interest in the place of somatostatin analogue therapy preoperatively, either as a short-term measure in the hope that surgical outcomes are improved or as a long-term alternative to surgery. Bevan et al. [67] and others have shown impressive tumour shrinkage in patients in whom somatostatin analogues have been used as first line therapy; far in excess of the modest impact of post-operative treatment. That said, there are little objective data that preoperative somatostatin analogue therapy improves the outcome of subsequent surgery although one randomized study suggested a higher rate of IGF-I normalization in patients with macroadenomas treated preoperatively with octreotide [68].

Both octreotide and lanreotide are available as monthly depot injections and the majority of data suggest they are of similar efficacy [69–71].

Pasireotide (SOM 230) is a novel somatostatin analogue SSA with high affinity for SST1, 2, 3 and 5. Some preliminary data suggest that it may be of value in patients with an inadequate response to octreotide, although this appears to be at the price of a significantly higher rate of impaired glucose tolerance and diabetes [72, 73].

Side-effects of somatostatin analogues include abdominal pain, diarrhoea, nausea and flatulence on initiation of treatment, which usually settle after a few weeks. Biliary tract abnormalities including gallstones, sediment, sludge, microlithiasis and dilatation have been reported in up to 50 % of patients, which rarely cause

problems during on-going treatment, although may cause symptoms on cessation due to the recovery of gall bladder peristalsis. SSAs inhibit insulin secretion and may result in hyperglycaemia. Asymptomatic sinus bradycardia and conduction abnormalities have been described and SSAs should be avoided in patients who are on drugs known to prolong the QT interval. Octreotide may alter the absorption of drugs such as oral hypoglycemic agents, calcium channel blockers or beta-blockers from the gastrointestinal tract.

### **Growth Hormone Receptor Antagonist: Pegvisomant**

Pegvisomant is a genetically engineered analogue of human GH that functions as a GH receptor antagonist [74, 75] by binding, but not activating, the pre-formed, cell surface, GH receptor dimer. The half-life of the analogue is the same as GH at approximately 15 min but is extended to >70 h by the addition of 4–5 5,000 Mwt polyethylene glycol moieties. Unlike other treatments for acromegaly it does not act on the pituitary adenoma to inhibit tumour growth or GH secretion. Feedback mechanisms mean GH levels increase with pegvisomant therapy but in the presence of the antagonist lacks biological activity, and IGF-I is the main measure of disease activity. Pegvisomant is detected by most commercial GH assays and therefore serum GH should not be routinely measured in patients on pegvisomant therapy, as results are likely to be prone to artefact and can be misleading.

In the defining prospective, placebo controlled study, pegvisomant normalized IGF-I in 89 % of patients at a dose of 20 mg/day [76]. The open-label extension study saw normalization of IGF-I in 97 % of patients using doses of up to 40 mg/day [77]. Data from the post-marketing surveillance database suggests that outside of studies the IGF-I normalization rate is only around 70 %, almost certainly due to a failure to adequately dose titrate patients [78].

The long half-life of pegvisomant means it is probably a once weekly, rather than daily medication although the current formulations (maximum 20 mg/mL) make the volume of injection a hindrance.

The place of pegvisomant in the treatment algorithm is in patients with persisting symptoms and elevated IGF-I despite surgery, possibly radiotherapy and maximum doses of somatostatin analogues. The dilemma is whether pegvisomant should be either added to ongoing or replace somatostatin analogue therapy. Several studies have addressed this issue [79] and suggest that the decision should be based on consideration of individual patient's circumstances. The factors to consider include the extent of the IGF-I response to somatostatin therapy, glucose tolerance (where somatostatin analogues can have a negative effect while pegvisomant can be expected to improve the situation) and tumour size, as somatostatin analogue-induced tumour shrinkage would obviously be a reason to persist with therapy. Monotherapy and combination therapy are both expensive but there is probably little to choose between the two in terms of cost.

Pegvisomant in combination with cabergoline has been shown to reduce the dose of the high-cost pegvisomant and therefore offers a more cost-effective option.

When clinical trials began there was a concern that the increase in GH levels could be a harbinger of subsequent tumour growth [77] but the evidence to date is very reassuring with only 3.2 % patients ( $n=1,288$ ) showing an increase in tumour size [80].

Elevation of liver enzymes (aspartate aminotransferase or alanine aminotransferase) of more than three times the upper limit of normal has been reported [76, 80]. This derangement resolves on discontinuation of the drug [81]. Current recommendations are to check liver function tests before starting the drug, monthly for the first 6 months and six-monthly thereafter, and initially six monthly and ultimately annual pituitary MR imaging [18, 82]. Lipohypertrophy has been reported at the injection sites [81] but in general the drug is well tolerated.

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## **Conclusion**

The last two decades have seen major advances in our understanding of the pathophysiology of GH-secreting adenomas, for example recognition

of the AIP gene, and in all modalities of treatment for acromegaly that are transforming the prognosis for patients once diagnosed. The greatest challenge remains the delay in diagnosis which results in most patients having been symptomatic for a decade before acromegaly is confirmed. Surgery by an experienced pituitary transsphenoidal surgeon is the appropriate initial treatment and thereafter the skill is in using the pharmaceutical options to achieve biochemical and tumour control with a minimum of adverse events and expense. Radiotherapy still has a part to play in a selected cohort of patients.

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Hypopituitarism is a complex medical condition with variable clinical manifestations associated with significant morbidity and mortality. The term describes the deficiency of one or more of the hormones of the anterior or posterior pituitary gland. The majority of patients with hypopituitarism have 3–5 hormones deficits.

Hypopituitarism affects approximately 4 out of every 100,000 individuals each year [1] with a prevalence of approximately 45 cases per 100,000 individuals. The causes, clinical features, diagnosis, management of hypopituitarism (including endocrine replacement therapy), interaction of hormone replacement, and long-term management are considered in this chapter.

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## Causes

There are numerous causes of hypopituitarism (Tables 8.1 and 8.2). The etiologic factors are determinants in the clinical presentation of this condition. For instance, pituitary apoplexy constitutes a medical emergency with the possibility of acute adrenal crisis and sudden loss of vision. On the other hand, functioning pituitary adenomas lead to a clinical picture that predominates the stigmata of the corresponding hormonal hypersecretion. Signs and symptoms related to local mass effect, including associated secondary hypothyroidism and hypocortisolism, may occur as a nonspecific presentation and remain unrecognizable for a long period of time.

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## Diagnosis

### Clinical Presentation

The clinical presentation of hypopituitarism is often vague and nonspecific, leading to a further delay in diagnosis. Nonspecific symptoms include a feeling of general poor health, increased lethargy, feeling cool, chronic tiredness, reduced appetite, weight loss, and abdominal pain [2, 3]. Hypopituitarism can sometimes develop acutely, leading to a rapid onset of symptoms (excruciating

**Table 8.1** Causes of Hypopituitarism

<i>Neoplasia</i>	<i>Vascular</i>
Pituitary adenoma	Pituitary tumor apoplexy
Pituitary carcinoma	Sheehan's syndrome
Craniopharyngioma	Intrasellar carotid artery aneurysm
Pituicytoma	
Fibroma	Subarachnoid hemorrhage
Glioma	
Meningioma	Ischemic stroke
Paraganglioma	<i>Genetic</i>
Teratoma	Combined pituitary hormone deficiencies
Chordoma	
Angioma	Isolated pituitary hormone deficiencies
Sarcoma	
Ependymoma	<i>Infectious</i>
Germinoma	Viral
Cysts	Fungal
Rathke's cleft and dermoid	Tuberculosis
Ganglioneuroma	Syphilis
Astrocytoma	Bacterial (Others)
Pituitary metastasis	<i>Primary empty sella functional</i>
<i>Brain damage</i>	
Surgery	Drugs
Radiotherapy	Glucocorticoid excess
Radiosurgery	Megestrol acetate
Traumatic brain injury (TBI)	Suppressive thyroxine treatment
<i>Infiltrative/inflammatory disease</i>	
Lymphocytic hypophysitis	Dopamine
Granulomatous hypophysitis	Anabolic sex steroids
Xanthomatous hypophysitis	GnRH agonists
Sarcoidosis	Nutritional
Langerhans cell histiocytosis	Obesity
Giant cell granuloma	Malnutrition
Wegener's granulomatosis	Caloric restriction
Hemochromatosis	Chronic/Acute critical illness
	<i>Idiopathic</i>

headache, meningism, and cardiovascular collapse) necessitating admission and intensive care management, as is often seen in patients with tumor apoplexy.

The signs and symptoms of underlying diseases can sometimes follow hypopituitarism [3]. Symptoms attributed to the local effects of tumoral masses in the sellar region with suprasel-

lar extension, such as headaches, rhinorrhea, and visual disturbances (typically bilateral hemianopsia, but can also occur as unilateral) frequently remain unrecognized by patients, mostly men, for a long period of time.

Deficits of anterior pituitary hormones may be secondary to hormone excess caused by functioning pituitary tumors, which produces a complex picture combining hormone excess and deficiencies, such as suppression of gonadotropins in hyperprolactinemia, growth hormone deficiency (GHD) caused by cortisol excess in Cushing's syndrome [4] or growth hormone (GH) secreting macroadenoma that causes acromegaly and hypogonadism [5]. The presence of central Diabetes Insipidus (DI) usually indicates a non-pituitary lesion affecting the hypothalamus or pituitary stalk. Preoperatively, pituitary adenomas rarely cause DI.

## Somatotropin Deficiency

### Children

GHD in childhood promotes short stature and delayed bone age with slow growth velocity. Idiopathic GHD is the most common etiology. GH does not appear to have a relevant role in fetal growth. Therefore, in general, children are born with normal length, weight, and general appearance. However, microphallus and cryptorchidism may be present, especially with gonadotropin associated deficiency. Prolonged jaundice, hypoglycemia-associated seizures (when GHD occurs in conjunction with Adrenocorticotropic Hormone (ACTH) deficiency), and midline abnormalities suggest a congenital etiology.

Recognition of GHD is more common from the first 12–18 months after birth, with slow growth as an early sign and a consequent downward shift in the normal growth curve. Children tend to present with adiposity around the trunk. They have immature body and facial traits, a high-pitched voice, prominent forehead, depressed mid-face development, delayed dentition, and small hands and feet.

**Table 8.2** Genetic forms of multiple pituitary hormone deficiencies

	HESX1	OTX2	LHX3	LHX4	SOX3	SOX2	PROPI	POU1F1
GH	+	+	+	+	+	+/-	+	+
LH/FSH	+/-	+/-	+	+/-	+/-	+	+	-
PRL	+/-	-	+	-	+/-	-	+	+
TSH	+/-	+/-	+	+/-	+/-	-	+	+/-
ACTH	+/-	+/-	+/-	+/-	+/-	-	+/-	-
ADH	+/-	-	-	-	+/-	-	-	-
Inheritance	AR/AD	AD	AR	AD	XL	AD	AR	AR/AD
Pituitary involvement	Normal/ Hypoplastic AP; normal/ectopic PP	Normal/hypoplastic AP; altered stalk; Ectopic PP	Hypoplastic, normal or enlarged AP	Normal/hypoplastic AP; normal or ectopic PP	Hypoplastic AP; Ectopic PP	Normal/ hypoplastic AP; Hypothalamic hamartoma	Hypoplastic, normal or enlarged AP and normal PP	Normal/ hypoplastic AP
Extra-pituitary phenotype	SOD; normal optic nerves	Anophthalmia or no ocular pathology; Chiari malformation	limited neck rotation or no; SD	Cerebellar anomalies; Chiari malformation	Variable learning difficulties; HCC	Anophthalmia; Microphthalmia; DD; SD; HCC; Aesophageal atresia	No involvement	No involvement

AD autosomal dominant, AP anterior pituitary, AR autosomal recessive, DD developmental delay, PP posterior pituitary, HCC hypoplasia of corpus callosum, SD sensorineural deafness, SOD septo-optic dysplasia, XL X-linked, + deficiency, - no deficiency

## Adults

The severity of the clinical manifestations of GHD in adults depends on the timing of onset. In general, patients present nonspecific symptoms, such as fatigue, decreased energy, low mood, and altered body composition with increased fat and decreased lean body mass and muscle strength, as well as reduced bone mineral density, compromised metabolism of glucose and lipids, and poor quality of life [6]. Childhood-onset GHD patients have a lower lean body mass, bone mineral content, and better quality of life compared to adult-onset GHD patients.

## Gonadotropin Deficiency

The clinical presentation of male hypogonadism depends on the time of onset of androgen deficiency. In men with recent onset hypogonadism, the physical examination is usually normal, while diminished facial and body hair, gynecomastia, and small soft testes are features of longstanding hypogonadism [2]. The principal signs and symptoms of androgen deficiency in men are loss of libido, decreased sexual potency, loss of body hair (axillary and pubic), infertility, and low bone mineral density. The threshold testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur and testosterone administration improves outcomes in the general population is currently not known [7].

Female adolescents have primary amenorrhea and lack of breast development, whereas in adult women, gonadotropin deficiency leads to reduced secretion of estradiol, resulting in infertility and oligo/amenorrhea. Low estrogen is also responsible for genital atrophy and decreased breast volume in chronic hypogonadism. There is a reduction of pubic and axillary hair, especially when concomitant dysfunction of the corticotropin axis is present.

At the prepubertal age, no obvious clinical signs or symptoms are present until the normal age of puberty onset (9–14 years in boys and 8–13 years in girls), when a lack of signs of normal pubertal development are then observed. It should be emphasized that micropenis with or

without associated cryptorchidism is an important clinical clue that suggests congenital hypogonadotropic hypogonadism (where there is lack of the normal fetal secretion and postnatal surge of gonadotropins) rather than acquired hypogonadotropic hypogonadism [8].

## Thyrotropin Deficiency

The clinical picture of central hypothyroidism is very similar to primary hypothyroidism, but is often milder. Symptoms include cold intolerance, dry skin, decreased appetite with mild weight gain, and fatigue [9]. The presence of goiter usually indicates primary thyroid disease. In children, decreased growth velocity with impairment of neurological development is an important sign.

## Corticotropin Deficiency

ACTH deficiency leads to decreased glucocorticoid levels. Mineralocorticoid secretion is preserved, since it is primarily modulated by the renin–angiotensin system. Hyperpigmentation is typical of primary adrenal disease and is absent in central disease. Symptoms of ACTH deficiency are largely nonspecific, including weakness, fatigue, anorexia, weight loss, arthralgia, postural hypotension, and tachycardia [10]. Hyponatremia, hypoglycemia, and eosinophilia may also occur. Ultimately, if left untreated, ACTH deficiency may lead to death due to vascular collapse, since cortisol is needed to maintain vascular tone. Mild ACTH deficiency may remain clinically unnoticed when cortisol production is sufficient for preventing symptoms in the absence of clinical stressors (e.g., infections). Hence, laboratory evaluation is recommended in all patients at risk of ACTH deficiency.

## Antidiuretic Hormone (ADH) Deficiency

ADH deficiency results in polyuria (urine volume >3 L/day in adults) and polydipsia. If the thirst mechanism is not present, as is the case in some

patients with hypothalamic lesions, then lack of polydipsia leads to a high risk of life-threatening dehydration and hypernatremia [11].

## Diagnostic Testing

The diagnosis of hypopituitarism can often be made through simultaneous measurements of basal anterior pituitary and target gland hormone levels. Each axis should be assessed in patients suspected of having partial or complete loss of pituitary function, because the impairment in these patients is often partial rather than complete.

Low or inappropriately normal serum levels of pituitary hormones in conjunction with low peripheral hormones indicate hypopituitarism. FSH, LH, estradiol (women), testosterone (men), prolactin, TSH, free thyroxine (FT4), 9 am cortisol, and insulin-like growth factor-I (IGF-I) tests form the baseline parameters to assess. In addition, dynamic studies are necessary in most cases for documenting hypopituitarism, particularly for assessing GH secretory reserve and the ACTH-adrenal axis (Table 8.3) [5].

## Somatotropin Deficiency

### Children

GHD in children is based on auxological data, which is considered the gold standard in such diagnosis [12]. An appropriate differential diagnosis must be performed ruling out other causes of growth failure, such as hypothyroidism, Turner syndrome, and systemic diseases.

Evaluation should be considered when patients present with one of the following conditions: (1) short stature of more than 2.5 standard deviations (SD) below the mean; (2) growth failure, which is defined as height velocity less than 2 SD below the mean for age; (3) a combination of less severe short stature (2–2.5 SD below the mean for age) and growth failure (growth velocity less than 1 SD); (4) clinical picture suggesting hypothalamic-pituitary dysfunction, such as hypoglycemia, micropallus, intracranial tumor, or history of cranial irradiation with decelerating

growth; and (5) evidence of deficiency in other hypothalamic–pituitary hormones [13].

The pulsatile nature and short half-life of GH preclude the random measurement of serum GH levels as a useful tool for diagnosing GHD. Thus, IGF-I and IGF-binding Protein 3 (IGFBP-3) are appropriate initial tests for GHD in children providing that conditions such as poor nutrition, hypothyroidism, and chronic systemic diseases are excluded. These hormones reflect an integrated assessment of GH secretion because of negligible diurnal variation [14].

IGF-I and IGFBP-3 measurements should be interpreted in relation to reference ranges that are standardized for sex and age. An important drawback to using serum IGF-I for GHD diagnosis is that its values are low in very young children and overlap in GHD patients and normal children. In this context, IGFBP-3 levels, which are less related to age, are more discriminatory than IGF-I levels at the lower end of the normal range [15].

These tests present less than adequate sensitivity, although specificity is high. Thus, in patients with severe GHD, IGF-I and IGFBP-3 levels are invariably reduced; On the other hand, patients with milder abnormalities of GH secretion demonstrate normal levels of IGF-I and its binding protein in a significant percentage of cases [16].

Despite these limitations, measurement of IGF-I and IGFBP-3 levels associated with provocative testing in an appropriate clinical context is now commonly performed when investigating GHD in childhood.

## GH Stimulation Testing in Children

Provocative GH testing has several caveats. They are not physiological, since the secretagogues used do not reflect normal GH secretion; the cutoff level of normal is arbitrary and the tests are age dependent. Furthermore, the tests rely upon GH assays of variable accuracy and are all uncomfortable, cumbersome, and risky for the patient [12, 17]. Therefore, there is currently no gold standard provocative GH test for GHD in children. As a result, subnormal responses to two secretagogues are necessary for diagnosis, with

**Table 8.3** Hormone testing for pituitary function

	Criteria for hormone deficiency
<i>Somatotropic axis</i>	
Baseline	
IGF-I	Low/low-normal
GH	No usefulness
Provocative tests	
Clonidine test (only for children)	<7–10 µg/L
Insulin tolerance test	Children: <7–10 µg/L
	Adults: <5.1 µg/L
	Transition period: <6.1 µg/L
GHRH-Arg test (only for adults)	Adults:
	Lean <11.5 µg/L
	Overweight <8.0 µg/L
	Obese <4.2 µg/L
Glucagon test	Transition period: <19.0 µg/L
	Children: <7–10 µg/L Adults: <2.5–3 µg/L
<i>Gonadotropic axis</i>	
Baseline	
Male	
Testosterone	Low
FSH/LH	Low or inappropriately normal
Female	
Estradiol	Low
FSH/LH	In younger women: low or inappropriately normal
	In postmenopausal women: inappropriately low
Provocative test	
GnRH	Not useful in adults
<i>Thyrotropic axis</i>	
Baseline	
Free T4	Low, low-normal
TSH	Low, normal or slightly increased
Provocative test	
TRH	Not useful
<i>Corticotropic axis</i>	
Baseline	
Cortisol (morning)	<3 µg/dL (<80 nmol/L)
	>18 µg/dL (>500 nmol/L): hypocortisolism excluded
ACTH (morning)	Low or normal
Provocative tests	
Insulin tolerance test	Peak Cortisol <18 µg/dL (<500 nmol/L)
250 µg ACTH test	Peak Cortisol <18 µg/dL (<500 nmol/L)
Overnight metyrapone test	11-deoxycortisol <7 µg/dL (<200 nmol/L), low cortisol
CRH (human or ovine)	ACTH: Peak <2–4× baseline
	Cortisol: Peak <20 µg/dL (555 nmol/L)
<i>Antidiuretic hormone</i>	
Dynamic test	
Water deprivation	Maximal Urinary Osmolality (MUO) <300 mOsm/kg/H <sub>2</sub> O plus >50 % increase in MUO after desmopressin (Complete DI)



**Table 8.4** Protocols of dynamic tests for investigation of anterior pituitary (GH and ACTH) and posterior pituitary (ADH) deficiencies

Provocative tests	Dosage	Time of hormone collection	Side effects/drawbacks
<i>GH</i>			
Clonidine (only for children)	5 µg/kg, up to 250 µg, PO	GH: 0, 30, 60, 90 min	Drowsiness; false negative results
Insulin tolerance test	Regular insulin 0.05–0.15 IU/kg, IV	GH: 0, 15, 30, 60, 90, 120 min	Severe hypoglycemia and medical surveillance required
Glucagon	0.03 mg/kg (up to 1 mg) IM/SC; if >90 kg, 1.5 mg	GH: 0, 60, 90, 120, 150, 180, 210, 240 min	Late hypoglycemia; very prolonged test; not well validated in adults
GHRH-ARG (only for adults)	GHRH (1 µg/kg, IV bolus) + Arginine (0.5 g/kg, up to 30 g, IV, over 30 min)	GH: 0, 30, 60, 90, 120 min	Very influenced by adiposity
<i>ACTH</i>			
ACTH <sub>1-24</sub>	250 µg IV/IM	Cortisol: 0, 30 and 60 min	Adrenal atrophy is required
Insulin tolerance test	Regular insulin 0.05–0.15 IU/Kg, IV	Cortisol: 0, 15, 30, 60, 90, 120 min	See above
Overnight metyrapone	30 mg/kg, PO, at midnight (maximum 3 g)	11-deoxycortisol and cortisol: 8 am	Limited availability; adrenal crisis
CRH (human or ovine)	1 µg/kg, up to 100 µg, IV	Cortisol and ACTH: 0, 15, 30, 60, 90, 120 min	Flushing; expensive
<i>Dynamic test</i>	<i>Procedure</i>		<i>Side effects/Drawbacks</i>
<i>ADH</i>			
Water deprivation	Nothing allowed by mouth; patient voids; weight is recorded; Serum Na <sup>+</sup> and urine Osm are measured at baseline. Weight is checked after each liter of urine is passed. In each voided urine, measure urine Osm and when two consecutive measurements differ <10 % and subject has lost 2 % of BW, plasma sample for Na <sup>+</sup> , Osm and VP should be drawn. DDAVP 2 µg IV/IM is administered and urine Osm and volume are measured every 30 min in the next 2 h. Dehydration is stopped if patient has lost >3 % of BW or if serum Na <sup>+</sup> becomes elevated.		Difficulties in differentiate partial hypothalamic DI from primary polydipsia

PO per oral, Osm osmolality, BW body weight, VP vasopressin

the exception of patients presenting with a central nervous system disorder, multiple pituitary hormone defects, or a known genetic defect. In these cases, one test is sufficient to establish the diagnosis [18].

These stimulation tests are performed after an overnight fasting. After the pharmacologic stimulus, serum samples are collected at intervals designed to capture the peak GH level. A “normal” response is defined by a serum GH concentration of greater than 7–10 mcg/L, although the ideal threshold may vary with the assay used. Of note, all patients should be euthyroid and should not be under supraphysiological doses of glucocorticoids before any testing is performed (Tables 8.3 and 8.4).

Clonidine, an  $\alpha$ -2 adrenergic receptor agonist, promotes GH release, mainly through GHRH secretion. It is a stronger stimulant for growth hormone release, and therefore false negative results can follow. On the other hand, children presenting with a GH subnormal response to such stimulus rarely secrete normal GH in response to any other stimuli [19]. The test commonly causes hypotension and drowsiness that may last for hours and promote late hypoglycemia.

Insulin-induced hypoglycemia is a potent stimulant of GH release and, therefore, the Insulin Tolerance Test (ITT) is among the most specific tests for GHD. However, safety concerns have prevented the widespread use of this test. The proposed mechanism by which hypoglycemia promotes GH secretion is through the

suppression of somatostatin tone and stimulation of  $\alpha$ -adrenergic receptors [20]. This test requires constant supervision by a clinician and is contraindicated in children less than 2 years of age.

Administration of glucagon promotes GH secretion through a poorly understood mechanism, with the activation of central noradrenergic pathways as a plausible hypothesis [21]. Glucagon presents mild and transient side effects, such as nausea, vomiting, and sweating, and therefore is a very good choice for infants and young children who are more susceptible to the risks of insulin-induced hypoglycemia.

### Adults

In adults, the clinical picture of GHD is subtle and nonspecific, and therefore the diagnosis relies on biochemical testing. Patients with structural hypothalamic and/or pituitary disease, surgery, or irradiation in these areas as well as TBI, SAH, or evidence of other pituitary hormone deficiencies should be evaluated for acquired GHD. Otherwise, the presence of three or more pituitary hormone deficiencies associated with a low IGF-I is highly predictive of GHD, in which case provocative testing is not necessary [22]. In addition, patients should receive adequate replacement of other deficient hormones before GH stimulation testing is performed.

### GH Stimulation Testing in Adults

ITT is considered the most validated test currently available and is the diagnostic test of choice for GHD in adults. However, it is contraindicated in patients with seizure disorders or ischemic heart disease and requires monitoring, even in healthy adults. Adequate hypoglycemia ( $<2.2$  mmol/L) is not always achieved, and therefore, larger doses of insulin up to 0.3 U/kg may be necessary in obese patients and those with fasting blood glucose above 5.5 mmol/L [23]. An assay cutoff of 5.1  $\mu$ g/L is recommended for diagnosis [22].

A GHRH and arginine test (GHRH-Arg test) is a very potent and reproducible test. Arginine potentiates the response to GHRH presumably through

the inhibition of hypothalamic somatostatin secretion [24]. This combined test is not affected by gender or age and shows few side effects with no hypoglycemia. On the other hand, the assay cutoff for GHD diagnosis depends on the body mass index (BMI) [25]. In addition, GHRH directly stimulates the pituitary, and patients with GHD of hypothalamic origin, mainly after radiotherapy, could present a falsely normal GH response [26].

Administration of glucagon allows for the assessment of GH and ACTH-cortisol reserves, and has few side effects with minimal contraindications. It is a good choice when other tests are unavailable or contraindicated. In adults, an assay cutoff between 2.5 and 3.0  $\mu$ g/L is recommended for GHD diagnosis [22].

### Transitional Period

In the transition period (i.e., after the cessation of linear growth and completion of puberty), the majority of GHD patients must be retested. Those patients with conditions causing multiple pituitary hormone deficiencies (MPHD) (i.e., three or more pituitary hormone deficits), can continue on GH therapy, but require determination of an adequate dose. Other patients without MPHD but who present with known mutations or irreversible structural hypothalamic-pituitary lesions/damage should be screened for serum IGF-I levels after terminating therapy for at least 1 month. IGF-I levels below  $-2$  SD are sufficient for GH therapy reinstatement. If the IGF-I level is within the normal range, then one provocative testing is mandatory for GH therapy in case of a subnormal response.

In the remaining patients, mostly with idiopathic causes, a serum IGF-I test and one provocative test must be performed, and in case of discordant results, a second provocative test is necessary for the diagnosis of persistent GHD [22, 27].

It is unclear whether different assay cutoffs should be adopted during this transitional period, as opposed to GHD assay cutoffs in adults. Some studies suggest that the assay cutoffs in these cases should be higher than for older adults, with levels of 6.1  $\mu$ g/L and 19.0  $\mu$ g/L for the ITT and GHRH-arg, respectively [28, 29].

## Gonadotropin Deficiency

In men, low or inappropriately normal levels of gonadotropins combined with low levels of serum testosterone are indicative of secondary hypogonadism. Semen analysis is indicated when considering fertility and may demonstrate a reduced sperm count or possibly azoospermia.

In younger women, oligo/amenorrhoea with low serum estradiol levels and low or inappropriately normal FSH and LH concentrations is consistent with secondary hypogonadism. In postmenopausal women, the absence of the normal rise of FSH and LH levels is sufficient for establishing a diagnosis.

In secondary hypogonadism, serum prolactin should always be measured to exclude hyperprolactinemia, which might occur for several reasons, such as prolactinomas, sellar and parasellar masses causing pituitary stalk compression, and use of drugs with antidopaminergic activity.

In adults, there is no usefulness in performing the gonadotropin-releasing hormone (GnRH) provocative test because it does not provide any additional information [5].

## Thyrotropin Deficiency

Evaluation of the thyrotrophic axis is based on the measurement of basal serum TSH and thyroid hormone levels. Central hypothyroidism is diagnosed when serum TSH levels are low or inappropriately normal coupled with low levels of serum free T4. Occasionally, TSH levels may be slightly elevated but usually remain lower than 10 mIU/mL. In these patients, the elevation of serum TSH is associated with decreased bioactivity due to increased sialylation [30]. In patients with concomitant GH and TSH deficiencies, serum-free T4 may be normal (usually at the lower tertile), decreasing only after GH replacement [31, 32]. More recently, it has been proposed that echocardiography can be useful in the evaluation of patients with hypothalamic-pituitary disease and free T4 levels within reference range, as some of these patients present

signs of tissue hypothyroidism, a condition that could be named “subclinical central hypothyroidism” [33].

The TRH stimulation test has been performed in the past to diagnose central hypothyroidism [34]. However, this test is not currently recommended due to a lack of accuracy [35].

## Corticotropin Deficiency

Cortisol secretion follows a circadian cycle, being highest in the early morning and lowest at midnight. Hence, a basal serum cortisol measurement may not reflect disturbances of the hypothalamus-pituitary-adrenal (HPA) axis. In addition, alterations in the levels of cortisol-binding globulin (CBG), which is frequently seen in clinical practice (e.g., higher levels of CBG, and consequently serum total cortisol, during oral estrogen treatment as a contraceptive) may also mask the diagnosis of central hypoadrenalism. Therefore, early morning serum cortisol (between 07:00 and 09:00) may be measured as a first step in the evaluation [10]. Stimulation tests are frequently required for corticotropic assessment. The most commonly used stimuli in clinical practice are insulin-induced hypoglycemia, Metyrapone, synthetic ACTH (ACTH<sub>1-24</sub>), and CRH (Tables 8.3 and 8.4).

Hypoglycemia is a potent activator of the HPA axis, and the ITT is usually regarded as the “gold standard” for diagnosis (see more details in “GH stimulation testing”).

ACTH<sub>1-24</sub> administration is currently the most commonly used test in clinical practice for assessing HPA axis. Adrenal atrophy is required for the test to be positive in cases of ACTH deficiency. Hence, this test should not be performed within 2 weeks of an insult to the hypothalamus or pituitary (e.g., pituitary surgery) [36]. A low-dose (1 µg) ACTH<sub>1-24</sub> test has been reported to induce improved sensitivity by some studies [37] but not others [38].

Metyrapone decreases serum cortisol by inhibiting the enzyme 11-beta-hydroxylase and this test is usually not performed due to limited availability of the drug.

CRH has been used to differentiate hypothalamic from pituitary disease in secondary adrenal insufficiency. However, CRH stimulation is not particularly useful in diagnosing secondary adrenal insufficiency because individual responses to exogenous CRH are extremely variable.

## ADH Deficiency

DI may be diagnosed with a proper clinical presentation, for example, in a patient with known pituitary/hypothalamic disease if other causes of polyuria (e.g., diabetes mellitus, use of diuretics) are excluded. Serum sodium is usually above the middle of the reference range, but hyponatremia is not seen in patients with an intact thirst mechanism. In situations where diagnosis is not clear-cut, a water deprivation test is warranted. Maximum urine osmolality is less than 300 mOsm/Kg H<sub>2</sub>O in patients with complete DI. In patients with subnormally elevated osmolality after water deprivation (300 mOsm/Kg < osmolality < 800 mOsm/Kg H<sub>2</sub>O), further steps are needed, including magnetic resonance imaging (MRI) of the hypothalamic-pituitary region and/or a therapeutic trial with Desmopressin [11].

## Imaging

MRI is currently the single best imaging procedure in the investigation for most sellar masses. After hypopituitarism has been confirmed, MRI should be performed to exclude tumors and other lesions of the sellar and parasellar region. When this is not possible, computerized tomography (CT) provides a suitable alternative. Micro- and macroadenomas of the pituitary as well as other sellar masses, such as craniopharyngiomas and meningiomas, usually take up contrast to a lesser degree than the normal pituitary. Craniopharyngiomas and even pituitary adenomas may have a partially cystic content and, therefore, have low-intensity signals. Hemorrhage has a high-intensity signal on both T1- and T2-weighted images. On the other hand, asymptomatic pituitary adenomas are found upon autopsy in approximately 11 % of

individuals. Such adenomas may also be commonly seen as incidental findings (incidentalomas) on head CT or MRI scans performed for other reasons [39].

Recent MRI studies of the pituitary in patients who had suffered a TBI demonstrated pathological changes consistent with vascular injury. In the acute phase, the pituitary glands of these patients are significantly enlarged and may also present other abnormalities, such as hemorrhage, infarction, and partial stalk transection [40]. In the chronic phase, patients often demonstrate pituitary volume loss or empty sella, perfusion deficits, or lack of a posterior pituitary signal. Such abnormalities were reported to occur in 80 % of patients with hypopituitarism compared to 29 % of those without hypopituitarism [41].

## Neuro-Ophthalmic Exam

Patients with a known pituitary tumor must be carefully followed for evidence of growth with early chiasmal-optic nerve compression. The frequency of visual evaluation must be individualized based on the size of the tumor and its relation to critical structures. Goldmann perimetry is useful in plotting the visual field defects and also assists in follow-up.

## Management

Understanding the underlying pathophysiology in each patient and recognizing the probability for recovery of function are among the most important issues to be emphasized in the management of patients with hypopituitarism. Treatment is based on the underlying disease that leads to pituitary insufficiency.

Pituitary tumors may be treated with medical therapy, surgery, radiotherapy, or a combination of these modalities depending on the tumor subtype and clinical presentation [5]. Whereas prolactinomas are almost exclusively treated with dopamine agonists, neurosurgical removal is indicated for most other pituitary sellar and parasellar masses. Infections

(e.g., meningoen­cephalitis, tuberculosis, or syphilis) are treated with antibiotics or antivirals and granulomatous infiltrations (e.g., sarcoidosis) are treated with immunosuppressants.

The goal of hormone replacement therapy is to achieve normal levels of the circulating hormones in order to restore normal physiology as close as possible and to avoid the symptoms of deficiency with minimal side effects. Target peripheral hormones, rather than deficient pituitary hormones, should be replaced, except for GH deficiency, ADH deficiency, and gonadotropins, when fertility is desired [5]. Hormone replacement therapy should be started as soon as the diagnosis of hypopituitarism is made (Box 8.1). It is very important to carefully evaluate whether hypopituitarism is likely to be reversible or whether it is permanent, thereby requiring life-long hormone replacement therapy.

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## Hormone Replacement Therapy

### Hyposomatotropism

#### Children

Childhood GHD should be treated as soon as possible in order to improve linear growth. The individual response to GH therapy is widely variable and unpredictable. Dosing is mainly based on weight and can range from 0.021 to 0.050 mg/kg/day (0.033 mg/kg/day is the most suitable initial dose) up to 0.1 mg/kg/day in adolescents. It should be given once a day by subcutaneous injection, and should be adjusted based on growth response and IGF-I levels [42, 43].

Therapy should be started as early as possible in order to achieve the best results in growth where patients can achieve height within the mid-parental target height [44].

GH therapy in children is safe and adverse events are uncommon. Idiopathic intracranial hypertension (pseudotumor cerebri) is a rare occurrence that tends to occur early in therapy, and if it occurs then drug discontinuation and subsequent cautious reintroduction is necessary. Some patients may present increased insulin

resistance, which appears not to translate into marked glucose abnormalities [45].

The goals of therapy are to achieve therapeutic levels of IGF-I that are slightly above the mid-normal range (approximately 1 SD above the mean) adjusted for age, pubertal stage, and growth velocity above the 75th percentile curve [46, 47]. An evaluation is performed 4 weeks after beginning treatment, and in case of an adequate IGF-I response, the length/height should be rechecked every 3–6 months and IGF-I levels should be rechecked every 6–12 months.

Caution is necessary with unmasking hypothyroidism after GH therapy as previously discussed. Thus, free T4 should be assessed every 3 and 6 months after initiation of this therapy and yearly thereafter.

#### Adults

In adults, GH dosing regimens are not weight-based as in children, but rather are initialized with a lower dose and then titrated according to clinical parameters and IGF-I levels. The recommended GH starting dose is 0.2–0.3 mg/day for most patients and 0.1–0.2 mg/day for the elderly patients that are more susceptible to adverse events linked to therapy [22]. A target for IGF-I levels is the upper half of normal range.

The most common side effects, which occur in 5–18 % of patients, are joint stiffness, peripheral edema, arthralgias, and myalgias. Carpal tunnel syndrome and increased blood pressure are infrequent, but when present, are related to supraphysiological doses in most cases. When this occurs, a reduction in the dose is appropriate [48].

Although there are no conclusive data of a GH role in the development or recurrence of malignant diseases, GH is contraindicated in adult patients with an active malignancy. A slight increase in the risk for DM has been observed with GH therapy, and therefore diabetic patients may require changes in the doses of current medications [22].

Adjustments should be performed every 1–2 months during dose titration. A clinical response, IGF-I levels, and side effects should guide the choice of dose. After titration, evaluation should be performed at 6 months intervals.

## Box 8.1 Hormone Replacement Regimens

### *GH deficiency*

*Adults:* GH therapy 0.1–0.2 mg in elderly; 0.2–0.3 mg in adults; 0.4–0.5 mg, SC, in younger people; adjustment based on clinical response, adverse effects, and IGF-I levels that should be maintained in the middle/upper half of the normal range.

*Children:* GH therapy 0.033 mg/kg/day and up to 0.1 mg/kg/day, SC, during puberty; adjustments based on growth response and IGF-I levels that should be maintained 1 standard deviation (SD) above the mean.

### *FSH/LH deficiency*

*Adult male:* 75–100 mg of testosterone enanthate or cypionate IM weekly or 150 mg every 2 weeks; one or two 5 mg nongenital testosterone patches applied nightly over the skin; 5–10 g of a 1 % testosterone gel applied daily over skin; 30 mg of bioadhesive buccal testosterone every 12 h. Other options: 2 % of testosterone topical solution, 2 % testosterone gel, oral testosterone undecanoate, injectable testosterone undecanoate, testosterone-in-adhesive matrix patch, and testosterone pellets.

*Infants/Pubertal development (boys):* Infants and children with micropenis, three courses of testosterone enanthate 25 mg IM monthly, and another three courses can be repeated if necessary. At 13 years of age, testosterone enanthate or cypionate 25–50 mg IM dosed monthly; increase dose every 6–12 months until the adult replacement level is achieved (3–5 years).

*Adult female:* Oral contraceptive (20–35 µg ethinyl estradiol), conjugated estrogen 0.625–1.25 mg, estradiol valerate 1–2 mg, or transdermal application of estradiol 50–100 µg/day. Add progestagen in case of an intact uterus.

*Pubertal development (girls):* At 11 years of age, conjugated estrogen (0.15 mg daily or 0.30 mg on alternate days), ethinyl estradiol 2.5–5 µg, or 17β-estradiol 5 µg/kg daily, or estrogen release patches 25 µg 17β-estradiol (0.08–0.12 µg/kg/day) can be subdivided into 6–8 fragments. After 6 months or in case of spotting or menstrual bleeding, cyclic progestagens should be added.

### *TSH deficiency*

*Adults:* Levothyroxine: initial dose: 75–125 µg/day in most cases (in elderly, start with 25 µg/day). Adjust the dose based on clinical response and serum free T<sub>4</sub> levels. Serum free T<sub>4</sub> levels should be in the upper half of the reference range (see text).

*Children:* <6 months: 8–10 µg/kg/day; 6–12 months: 6–8 µg/kg/day; 1–5 years: 5–6 µg/kg/day; 6–12 years: 4–5 µg/kg/day

### *ACTH deficiency*

*Adults:* Hydrocortisone three times a day: more commonly 10 mg early morning, 5 mg mid-day, and 5 mg early evening; prednisolone 2.5–5.0 mg early morning; prednisone, 2.5–5.0 mg/day. Adjustment based on clinical assessment. Double or triple the oral dose in case of exercise, or mild febrile disease. Use parenteral (IV/IM) dose if vomiting or diarrhea occur or if surgery is performed (hydrocortisone, 200–300 mg/day in 3–4 divided doses). DHEA 25–50 mg/daily as a trial in symptomatic women.

*Children:* oral hydrocortisone 10–24 mg/m<sup>2</sup>/day or cortisone acetate 13.5–32 mg/m<sup>2</sup>/day or prednisolone 3–5 mg/m<sup>2</sup>/day; dexamethasone usually avoided.

### *ADH deficiency*

*Adults:* Desmopressin: start with 5–10 mcg as a single dose at night before the patient goes to sleep. Increase until there is no nocturia (increments of 5–10 mcg). Add a morning dose if bothersome polyuria present during the day. Eventually, another dose can be given during the afternoon. Equivalence of nasal solution to pills: 2.5–5.0 mcg (nasal)=0.1 mg (pill). Dose titration is needed if preparation is changed.

*Children (below 12 years of age):* Same initial doses of Desmopressin, but maximum daily doses are 30 mcg (nasal) and 0.8 mg (oral).

## Transitional Period

In the transition phase, the recommended dose is 0.4–0.5 mg/day with the goal of achieving IGF-1

levels between 0 and +2 SD with adjustments made at 1–2 month intervals. Reassessment should be made every 6 months thereafter until the patient is in their mid-twenties [22, 27].

## Hypogonadism (in the Adult Female)

Estrogen deficiency requires replacement for the relief of symptoms, such as loss of libido and dyspareunia as well as for the prevention of osteoporosis and premature cardiovascular disease. Epidemiological studies in women with anterior pituitary deficiency have demonstrated excessive cardiovascular mortality in untreated versus treated hypogonadism [49]. Thus, it is strongly recommended to replace sex steroids in younger women until the average age of menopause is reached (approximately 52 years of age in healthy subjects). On the other hand, findings of large studies of sex hormone replacement therapy in non-pituitary postmenopausal patients have shown an increased risk of cardiovascular and neoplastic diseases. Therefore, termination of sex hormone substitution in hypogonadal women after the average menopause age is recommended [50, 51].

The biological potency of 20 µg ethinyl estradiol, 1.25 mg conjugated estrogen, and 100 µg transdermal 17β-estradiol is comparable [52]. In premenopausal women, an oral contraceptive containing 20–35 µg ethinyl estradiol is an effective form of replacement therapy. Alternatively, oral estrogen preparations (conjugated estrogen 0.625–1.25 mg daily or estradiol valerate 1–2 mg) given cyclically or continuously with a progestagen can be administered. Transdermal application of estradiol (50–100 µg/day) is preferred over oral preparations because it avoids hepatic first-pass metabolism. In addition, the transdermal preparation minimizes the synthesis of procoagulatory factors and acute phase proteins, which are potential vascular risk factors [53], and eliminates the growth-hormone resistant effects of estrogen on IGF-I production in the liver [54]. All women who have an intact uterus should receive concomitant progesterone therapy. Breast cancer is clearly an absolute contraindication for sex steroid replacement therapy.

## Pubertal Development

The goal for therapy in this case is to approximate normal development, and the appropriate age for

intervention is around the chronological age of 11 years. Conjugated estrogens (initial dose 0.15 mg daily or 0.3 mg on alternate days), ethinyl estradiol (2.5–5 µg daily), or 17β-estradiol (initial dose 5 µg/kg daily) may be administered, and the dose should be gradually increased every 6–12 months over the following 2–3 years until the adult replacement dose is reached. After 6 months of therapy or in case of spotting or menstrual bleeding, cyclic progestagens (usually medroxyprogesterone 5–10 mg daily or norethisterone 0.7–1.0 mg daily) should be added for 12–14 days every month [55].

Estrogen-release patches offer an alternative treatment option. The smallest commercially available patch releases 25 µg 17β-estradiol daily. The patch can be divided into six to eight fragments, and each fragment allows a release of 0.08–0.12 µg/kg daily. Application of the patch may be limited to nighttime in order to mimic the pattern of estrogen secretion that is predominantly nocturnal during the initiation of puberty [56]. The dosage should be increased every 6–12 months until the adult replacement dosage is achieved.

## Fertility Treatment

Pulsatile GnRH is mostly used for ovulation induction in patients with hypothalamic hypogonadotropic hypogonadism and normal gonadotropin levels. However, such therapy should only be performed at centers with extensive experience in ovarian stimulation techniques.

Gonadotropin therapy is indicated in patients with gonadotropin deficiency or GnRH resistance, but can also be used in patients with GnRH defects [57]. Ovulation induction is initiated with 75 IU daily of a preparation containing only FSH or a mixture of FSH and LH (human menopausal gonadotropins). Careful ultrasound monitoring is recommended to ensure that only one or two follicles develop in order to prevent ovarian superstimulation and prevent multiple pregnancies. Once a follicle has become mature, a single dose of 5,000 IU of human chorionic gonadotropin (hCG) is administered to stimulate ovulation, which occurs within 36–48 h of administration.

Conception occurs in 5–15 % of cycles and cumulative conception rates average between 30 and 60 % [57].

### **Hypogonadism (in the Adult Male)**

The aim of androgen substitution is to restore the serum testosterone concentration to the normal range (in the mid-normal range) in order to maintain secondary sexual characteristics, prevent loss and optimize bone mass, and improve sexual function [7].

The route of delivery depends on availability, patient preference, consideration of pharmacokinetics, treatment burden, and cost. Testosterone therapy is contraindicated in patients with prostate cancer, untreated severe obstructive sleep apnea, and uncontrolled or poorly controlled heart failure [7].

### **Oral Testosterone**

Oral testosterone undecanoate is commercially available in many countries under various brand names in 40 mg capsules, but is not available in the United States. It is absorbed through the lymphatic system and bypasses the portal vein due to esterification at the 17 $\beta$  position. The daily dose is 80–240 mg given throughout the day with meals. However, this drug has low bioavailability and substantial interindividual and intraindividual variability in absorption [58]. Therefore, it is more suitable for patients who cannot tolerate transdermal or intramuscular administration.

### **Intramuscular Depot**

Testosterone enanthate and testosterone cypionate are 17 $\beta$  esters of testosterone that have been the standard preparations for testosterone treatment for decades and have been proven to be safe with few unwanted side effects. Both esters are more lipophilic than native testosterone and have a long half-life and duration of action.

After intramuscular administration of testosterone enanthate, serum testosterone peaks to maximal supraphysiological levels in approximately 10 h, followed by a gradual decline to low normal or even subnormal levels [59]. Intramuscular doses of testosterone enanthate or cypionate from 100 mg/week or 150–200 mg every 2 weeks are biologically effective. Serum testosterone should be monitored between mid-way injections aiming at a serum level between 350 ng/dL (12–3 nmol/L) and 750 ng/dL (24–5 nmol/L). Some clinicians prefer to monitor serum testosterone levels immediately prior to the next injection with a goal of achieving a level in the low normal range. Dose adjustment is performed by varying injection intervals or injection dosage.

Testosterone undecanoate (Nebido<sup>®</sup>) is another ester of testosterone that has a markedly longer half-life (34 days) and duration of effect than testosterone enanthate and cypionate. Intramuscular injection of testosterone undecanoate 1,000 mg every 3 months leads to constant physiological serum testosterone levels without the undesired initial peak in drug concentration observed with the other depot formulations. A reduction in the injection interval between the first and second administration is recommended [60] and with this loading dose, sufficient steady state testosterone levels may be achieved more rapidly. Serum testosterone should be monitored at the end of the injection interval with the goal of achieving a serum level of testosterone in the mid-normal range. Dose adjustment is performed by varying the injection intervals.

### **Transdermal Systems**

Transdermal systems are a popular treatment modality for hypogonadal men. Transdermal gel and patches provide a useful delivery system for normalizing serum testosterone in these patients [61]. The transdermal gel has the best pharmacokinetic properties of all the available formulations and can achieve stable serum testosterone concentrations within the normal range using a noninvasive



topical application that is applied once a day on non-pressure areas of the body. Potential limitations of transdermal systems include a high rate of skin irritation observed with patches and the possibility that the testosterone gel may be transferred to other individuals through skin contact [62]. Four testosterone gels are currently available in United States, including AndroGel<sup>®</sup>, Testim<sup>®</sup>, Axiron<sup>®</sup>, and Fortesta<sup>®</sup>. A multicenter study conducted by Swerdloff et al. [63] (Testosterone Gel Study Group) showed that a daily transdermal application of a hydroalcoholic gel containing 1 % testosterone (AndroGel<sup>®</sup>) at 5.0 and 10.0 g of gel (equivalent to 50 and 100 mg) increased serum testosterone levels in hypogonadal men to within the normal range. Treatment should be started with 5.0 g and adjusted as necessary up to a maximum of 10.0 g. Testim<sup>®</sup> is another brand of hydroalcoholic gel with the same concentration.

The 2 % formulation of testosterone topical solution (Axiron<sup>®</sup>) is a non-occlusive topical formulation administered to the axilla, instead of the hands. A multicenter study conducted by Wang et al. [64] in hypogonadal men treated with 30–90 mg of this preparation showed that application of the gel restored physiological testosterone levels in 84.8 % of treated patients. This finding is similar to results previously reported with testosterone gel and mucoadhesive buccal therapies. The suggested dose of Axiron<sup>®</sup> is 60 mg (30 mg applied to each axilla once a day), with adjustment of the dose ranging from 30 to 120 mg, as determined by the serum testosterone concentration.

A novel 2 % testosterone gel for the treatment of hypogonadal male (Fortesta<sup>®</sup>) is also supplied in a metered dose pump, which is applied to the front and inner thighs. A multicenter study [65] in hypogonadal men followed for 90 days demonstrated that a single daily dose of this preparation restored normal levels of testosterone in more than 75 % of hypogonadal patients, with a low risk of supraphysiological testosterone levels. The recommended starting dose is 40 mg once a day (2 g/2 mL of gel) with adjustment of the dose ranging from 10 to 70 mg, as determined by the serum testosterone concentration.

The transdermal system patch (Androderm<sup>®</sup>) delivers approximately 5 mg of testosterone every 24 h and results in normal serum testosterone concentrations in most hypogonadal men [66]. The application of one or two testosterone patches is recommended to be applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas. Testosterone serum levels can be assessed 3–12 h after the application of the patch. The dose should be adjusted to achieve testosterone levels in the mid-normal range. The scrotal patch is no longer available in the United States.

Testosterone in an adhesive matrix patch is now available in many countries. The recommended regimen consists of 2×60 cm<sup>2</sup> patches that delivers approximately 4.8 mg of testosterone per day and lasts for approximately 2 days. However, some patients experience skin irritation with this preparation [7].

### **Buccal Tablet**

A controlled release testosterone buccal system (Striant SR<sup>®</sup>) contains 30 mg of testosterone and mucoadhesive excipients, which rapidly adhere to the buccal mucosa and slowly form a gel. Transbuccal delivery of testosterone substantially circumvents hepatic first-pass metabolism. A study by Wang et al. [67] demonstrated that the administration of this preparation maintained serum testosterone concentrations within the normal range in most hypogonadal men. The recommended dose is 30 mg applied to the buccal region twice a day. Testosterone serum levels can be assessed immediately before or after application of the fresh system. Gum-related adverse events occurred in 16 % of treated subjects.

### **Pellets**

Subcutaneous pellets (Testospel<sup>®</sup>) provide stable physiological testosterone levels, but a minor surgical procedure is required for administration [68]. The pellets are implanted into the subdermal fat of the lower abdominal wall, buttock, or thigh.

The dose and regimen vary with formulation. The manufacturer recommends implantation of three to six 75 mg pellets every 3–6 months [7]. Extrusion of the pellets and infection are the main risks of this treatment.

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## Monitoring During Androgen Therapy

Men younger than 40 years of age may not need prostate monitoring as they are at low risk for the development of prostate cancer. In men 40 years of age or older with a baseline prostatic specific antigen (PSA) level greater than 0.6 ng/mL, rectal digital examination should be performed before initiating treatment, and PSA levels should be checked 3–6 months after the start of treatment and annually thereafter. A urological consultation is necessary if there is an increase in serum PSA concentration to a level greater than 1.4 ng/mL within any 12 month period of testosterone treatment. Hematocrit should be checked at baseline, at 3–6 months after the start of therapy, and annually thereafter. If the hematocrit is greater than 54 %, then the treatment should be stopped until it decreases to a safe level [7].

## Infants/Pubertal Development

Infants and children with micropenis (penile length less than 2.5 cm at birth and in infancy) related to congenital hypopituitarism may be treated with three courses of testosterone enanthate 25 mg given IM each month with the goal of increasing penis size. If the desirable increase in penile length (>0.9 cm) has not occurred, then another three course trial can be repeated [8].

There is no general consensus regarding the best time to induce pubertal development. An acceptable proposal may be to induce pubertal development at 13 years and obtain a slow and progressive increase. A monthly dose of testosterone enanthate or cypionate 25–50 mg IM may be used. The dose should be kept as low as possible in order to preserve maximal growth potential.

The dose should be increased every 6–12 months until reaching the adult replacement therapy within 3–5 years [57].

## Fertility Treatment

In secondary hypogonadism, spermatogenesis and fertility can be induced. Men with prepubertal onset hypogonadism are more likely to require replacement of FSH as well as LH, whereas men with postpubertal onset are more likely to require replacement of LH only.

The classical gonadotropin regimen combines hCG and human menopausal gonadotropin (hMG) given as IM or subcutaneous (SC) injections, depending on the available preparation [69]. After stopping testosterone treatment, hCG can be used initially at a dose of 2,000 IU twice a week to stimulate spermatogenesis. The dose is titrated against testicular volume and serum testosterone, which should be measured every 1–2 months, with the goal of achieving levels between 400 and 900 ng/dL within 3–4 months after initiating treatment. Some patients require as little as 500 IU per dose, while other patients need as much as 10,000 IU per dose. Sperm count is measured every 2–4 weeks, but the value is not used to adjust the hCG dose. Most patients who eventually reach a normal sperm count (over 20 million/mL) do so within 6 months, but some require 12–24 months. The addition of hMG should be considered if the sperm count does not reach one-half of the normal level within 12–24 months. The pharmaceutical preparation of hMG contains FSH and is used to replace FSH for stimulating spermatogenesis in men who are infertile due to secondary hypogonadism. Recombinant human FSH is also available, but has not been as well studied in men and is more expensive. FSH appears to be necessary for the initiation of spermatogenesis, but not for its maintenance or reinitiation. Therefore, for patients with prepubertal onset of secondary hypogonadism, the treatment should be started with both hCG 2,000 IU and hMG three times a week while titrating hCG doses based on serum testosterone levels.

## Thyrotropin Deficiency

Levothyroxine is the replacement of choice for central hypothyroidism [70]. Most patients use 75–125 mcg/day of L-T<sub>4</sub> (for pediatric dosages, see [Box 8.1](#)). Laboratory monitoring of serum-free T<sub>4</sub> levels should be performed. The FT<sub>4</sub> levels should remain in the upper half of the reference range for patients with concomitant untreated GH deficiency in order to ensure adequate replacement [31]. In eusomatotropic patients, the FT<sub>4</sub> levels should be in the mid-normal reference range [31, 71] (see “Hormone Replacement Therapy Interactions” below).

## ACTH Deficiency

Glucocorticoid replacement is a priority because its deficiency is potentially life-threatening. Replacement therapy should be initiated before the beginning of thyroxine and/or GH replacement, since these latter treatments may precipitate adrenal crisis. There is no consensus on the best glucocorticoid replacement regimen [10]. Many centers use hydrocortisone (15–20 mg/day) in divided doses in an attempt to mimic circadian variation (e.g., 10–15 mg in the morning and 5 mg in the early afternoon; see [Box 8.1](#)). Equivalent doses of prednisone, dexamethasone, or cortisone acetate have also been used. Approximate equivalent doses to 20 mg of hydrocortisone include cortisone acetate, 25 mg, prednisone, 5 mg, and dexamethasone, 0.75 mg. Mineralocorticoid is not required in ACTH deficient patients, since its secretion is under the control of the renin-angiotensin system. For children, hydrocortisone is usually the glucocorticoid of choice (10–24 mg/m<sup>2</sup>/day in divided doses). Prednisolone (3–5 mg/m<sup>2</sup>/day) is also used, albeit less frequently. Due to its higher potency and possible negative effects on growth, dexamethasone is avoided during childhood.

As a general rule, during acute illness, the usual glucocorticoid replacement dose is increased two to three times over a course of at least 3 days or more, if needed. If patients cannot take oral glucocorticoids or experience severe illness, then in

IV/IM hydrocortisone is given as 200–300 mg/day in 3–4 doses (e.g., 50 mg every 6 h) [10, 72].

Adult women with hypopituitarism show decreased levels of androgens, including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), androstenedione, and testosterone. Some studies on DHEA replacement therapy to these patients have shown beneficial results on quality of life as well as improved mood and sexual function [73–76], whereas other studies have not shown such benefits [77, 78]. A meta-analysis that included randomized studies on the effect of DHEA replacement therapy on the quality of life of primary or secondary adrenal insufficient patients showed a small improvement in quality of life and depression, but no effect on anxiety and sexual well-being [79]. In the same meta-analysis, the most commonly reported side effects were greasy skin, hirsutism, acne, scalp itching, and increased apocrine sweat secretion and odor [79]. However, to date there is insufficient evidence to recommend routine DHEA replacement to these patients [72]. Moreover, in many countries, DHEA is only available as a dietary supplement, and therefore there are often variable and unreliable amounts of the drug in each pill. When DHEA is replaced, the usual dosage ranges from 25 to 50 mg in a single morning dose [80]. Clinical effects are observed only after several weeks of treatment. Monitoring should include measurement of DHEA-S (24 h after the previous dose) as well as free testosterone or total testosterone with sex hormone-binding globulin (SHBG) and estimation of free testosterone. If side effects are observed, then the dosage may be decreased by 50 %.

## ADH Deficiency

Since polyuria and nocturia impair the quality of life, Desmopressin, a vasopressin analogue, should be given to most patients with DI [81]. Desmopressin is usually started as a single dose at night before the patient goes to sleep (e.g., 1 puff), which is increased until nocturia is controlled. A second dose (in the morning) and less commonly a third dose (in the afternoon) may be

added as needed. Desmopressin is usually available as nasal spray, with one puff delivering 10 mcg. It is also available as a pill at a concentration of 0.1 mg per dose. In the inpatient setting, Desmopressin may also be given intravenously or subcutaneously at a dosage of 2–4 mcg/day in two divided doses.

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## Hormone Replacement Therapy Interactions

A critical aspect in the management of patients with hypopituitarism is the interplay between different replacement therapies. Remarkably, GH status impacts thyroid and adrenal replacement, and estrogen influences growth hormone dosages.

GH increases the conversion of T<sub>4</sub> to T<sub>3</sub> [31]. Hence, patients with combined and untreated GH and TSH deficiencies may show normal serum T<sub>4</sub> levels, usually at the lower tertile, which masks the diagnosis of central hypothyroidism. Serum T<sub>4</sub> levels fall below the normal range only after GH replacement in these cases [32]. On the other hand, a decrease in serum T<sub>4</sub> levels after GH replacement should be evaluated carefully, since T<sub>3</sub> levels usually concomitantly rise. If serum T<sub>4</sub> levels fall to the mid-normal range, an increase in the dosage of levothyroxine is usually not necessary. Additionally, during concomitant GH and levothyroxine replacement therapy, serum T<sub>3</sub> measurements may help to detect thyroxine over replacement [71].

In contrast to the action of GH on thyroid axis, GH enhances the conversion of cortisol to the biologically inactive cortisone through 11 $\beta$ -hydroxysteroid dehydrogenase type 1 [82]. Therefore, GH replacement may induce glucocorticoid insufficiency. This effect has been observed in patients with multiple pituitary deficiencies [83], but not in patients with isolated GH deficiency [84].

Oral estrogen replacement decreases the effect of GH on hepatic tissue, which consequently decreases IGF-I levels. Thus, patients on oral estrogen should have their dosage of GH increased [52, 85]. Since this effect is not observed in

patients on transdermal estrogen due to lower concentrations of estrogen in the liver, this mode of administration is usually preferred in GH-deficient patients.

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## Long-Term Management

While radiotherapy is associated with progressive hypopituitarism, in the case of a pituitary tumor, even if hypofunction is present before surgical treatment, pituitary function should be reassessed postoperatively, as nearly as 50 % of pituitary deficiencies will resolve. Lifelong substitution therapy may thus not be necessary.

There is no evidence that GH replacement therapy is associated with the development of cancer, although the association of IGF-I levels and cancer in epidemiological studies has been explored. In addition, the evidence linking GH replacement therapy in GHD patients with the reversal of the highest rates of mortality observed in hypopituitarism is inconclusive.

More studies are needed in order to determine whether testosterone replacement in hypogonadal men increases the risk of developing or converting histological prostate cancer to the clinical form.

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## Potential Future Therapy

The presence of stem cells in the pituitary gland, which can give rise to all pituitary hormone cells, implies that these cells can be replaced after being lost or damaged. These stem cells could be of great usefulness in the treatment of hypopituitarism and may also have utility in the long-term management of pituitary deficiencies [86].

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## Aetiology

Exogenous CS includes primarily the administration of glucocorticoids as medical therapy for autoimmune and dermatological diseases, asthma, atopic reactions, and some cancers, and the less common iatrogenic adrenocorticotropin (ACTH) administration and the factitious auto-administration. Any topical, inhaled or injected corticosteroids administration has to be meticulously identified from the drug history [2].

Establishing the precise cause of endogenous CS remains challenging since it shares many clinical features with other common conditions. ACTH-dependent CS (80–85 %) includes mainly the ACTH-secreting pituitary tumours [Cushing's disease (CD)] (80 %), and both ectopic ACTH (20 %) and corticotropin-releasing hormone (CRH) (<1 %) syndromes (ECS) [1]. Corticotroph hyperplasia has been also described, but seems rare in large surgical series and we doubt its true existence [3]. CD is mainly caused by

microadenomas (<1 cm in diameter) and less by macroadenomas (5–10 %), with or without extrasellar extension or invasion; pituitary corticotroph carcinomas defined by extra-pituitary metastases are extremely rare [3, 4]. The molecular pathogenesis of corticotroph adenomas and carcinomas remains unknown but almost always has a monoclonal origin [5, 6]. On the other hand, the tumours that are more frequently associated with ECS are those arising from the lung, small-cell lung carcinoma (SCLC) (3.3–50 %) and neuroendocrine tumours (NETs) such as bronchial carcinoids (5–40 %), but can include pancreatic (7.5–25 %) or thymic carcinoids (5–42 %), pheochromocytomas (5 %) and medullary thyroid carcinoma (MTC) (2–8 %), while in a 12–37.5 % the tumour cannot be identified [7]. ECS is almost associated with tumours sited in the thorax and the neck, and in only one-third in the abdomen [8]. A further classification regards the identification of the primary site of the source of ECS [9], resulting in *overt* ECS when the tumoral source is present, *covert* ECS when the tumour is identified in a later evaluation or follow-up, and *occult* ECS when the tumoral source cannot be identified [7]. Adrenal rest tissue in the liver, in the adrenal beds, or in association with the gonads, may also produce hypercortisolaemia, usually in the context of ACTH-dependent disease after adrenalectomy [3].

ACTH-independent CS (20 %) is caused by unilateral adrenocortical tumours or bilateral adrenal hyperplasia or dysplasia. The most common pathology is a cortisol-secreting adrenal adenoma (60 %) or carcinoma (40 %); rarely

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ACTH-independent bilateral macronodular adrenal hyperplasia (AIMAH), primary pigmented nodular adrenal disease (PPNAD), micronodular adrenal disease (<1 %) which may be sporadic or associated with Carney complex, bilateral nodular adrenal disease in McCune-Albright syndrome (<1 %), and constitutive activation ACTH receptor by missense mutation (<1 %) [1, 3]. An increased number of eutopic receptors or aberrant receptors such as gastric inhibitory peptide (GIP) receptors have been found to be expressed in adrenal nodules associated with AIMAH, resulting in the food-dependent CS where GIP receptors are activated after a meal causing hypercortisolaemia [10]. More lately, other aberrant receptors such as vasopressin,  $\beta$ -adrenergic, luteinising hormone/human chorionic gonadotropin, serotonin, angiotensin, leptin, glucagon, interleukin-1 and thyroid stimulating hormone (TSH) have also been described [3]. In McCune-Albright syndrome, adrenal dysplasia is caused by an activating mutation at codon 201 of the  $\alpha$ -subunit of the G-protein stimulating cyclic adenosine monophosphate (cAMP) formation resulting in constitutive activation of adenylate cyclase leading to nodule formation and hypercortisolaemia [11]. In PPNAD, the adrenal glands may be of small or normal size with cortical micronodules (2–3 mm) that may be dark or black in colour mostly in the context of Carney complex where the tumour suppressor gene *PRKAR1A* (type 1A regulatory subunit of protein kinase A) has been shown to be mutated in approximately half of patients. In isolated cases, mutations in phosphodiesterase 11A (*PDE11A*) gene have demonstrated as well as a missense mutation of the ACTH receptor resulting in its constitutive activation, all resulting in ACTH-independent CS [3].

Finally, it is of interest to refer to medical conditions mimicking clinically CS features [12] along with mild biochemical evidence of hypercortisolaemia which remains under a physiological feedback hormonal control, so-called pseudo-Cushing (PC); these entities resolve after the resolution of the pre-disposing condition or require a close follow-up if symptoms and signs increase [1]. These states include the metabolic syndrome, polycystic ovarian syndrome, severe

obesity (as opposed to mild obesity where urinary free cortisol may be reduced), poorly-controlled diabetes, late pregnancy, psychiatric disorders (depression, anxiety disorder), alcoholism, anorexia nervosa, and generalised resistance to glucocorticoids [13–16]. It is thought that higher brain centres stimulate CRH release in these conditions, with subsequent activation of the entire hypothalamo-pituitary-adrenal (HPA) axis. Therefore, distinguishing CS from a PC state is a major clinical challenge for the endocrinologist.

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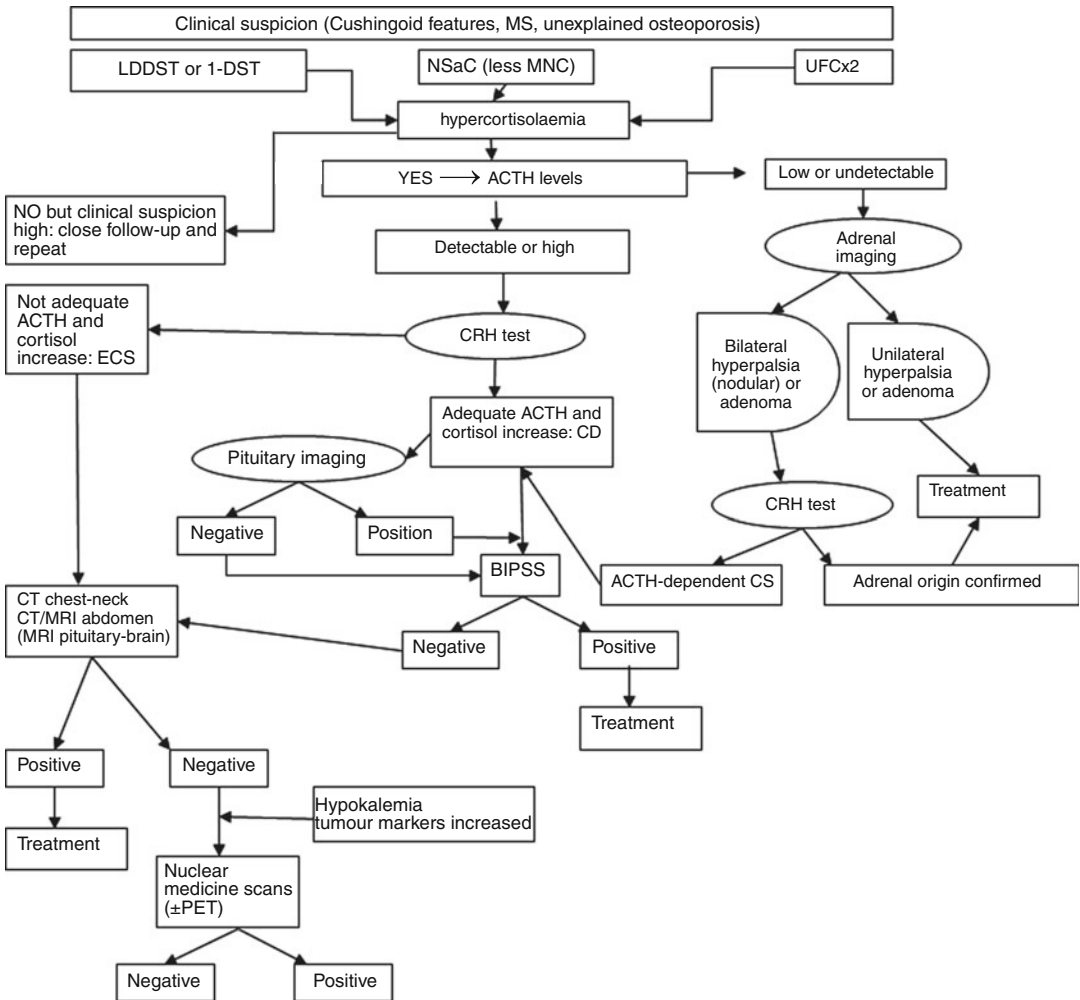
## Epidemiology

Endogenous CS seems to have an overall incidence of 2.3 per million per year with an incidence of 1.2–1.7 per million per year for CD, 0.6 per million per year for adrenal adenomas, and 0.2 per million per year for adrenal carcinomas, while other CS types are extremely rare [17]. CD is more common in women and between the ages of 25–40 years of age, while ECS is more common in men, and usually presents one decade older than in CD after the age of 40 years [7]. Adrenal adenomas occur most often around 35 years of age and are significantly more common in women, with an incidence of approximately 0.6 per million per year [3]. Adrenal carcinoma is slightly more common in women, and has a bimodal age distribution, with peaks in childhood and adolescence and then later in life [1, 18]. Regarding AIMAH, most cases are sporadic with a few familial cases [3].

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## Key Points to the Diagnosis and to the Differential Diagnosis (Fig. 9.1)

The most important step for the diagnosis of CS is the clinical suspicion along with a detailed past medical and drug history [1]. A vast range of signs, symptoms and other abnormalities along with a wide range of severity can be seen in CS (Fig. 9.1). When the presentation is florid including central obesity with limb wasting and muscle weakness, a plethoric face with hirsutism and frontal balding, spontaneous bruising along with metabolic



**Fig. 9.1** Diagnostic workup in Cushing's syndrome. *ACTH* adrenocorticotropic, *BIPSS* bilateral inferior petrosal sinus sampling, *CRH* corticotropin releasing hormone, *CD* cushing's disease, *CT* computed tomography, *ECS* ectopic Cushing's syndrome, *LDDST* low-dose dexameth-

asone test, *NSaC* night salivary cortisol, *MRI* magnetic resonance imaging, *MS* metabolic syndrome, *MNC* midnight cortisol, *PET* positron emission tomography, *UFC* 24 h-urinary free cortisol, *1-DST* 1 mg overnight dexamethasone test

abnormalities (hypertension, prodiabetes or diabetes) and osteoporotic fractures, then the diagnosis is straightforward. Protein wasting, thin skin in the young, easy bruising, and proximal muscle weakness most reliably distinguish CS from PC. In addition, while specific clinical features may suggest one rather than another aetiology, the degree of hypercortisolaemia seems to be the major determinant of the clinical features rather than its duration [7, 9]. Severe hirsutism and virilisation strongly suggest an adrenal carcinoma [3]. A gradual onset of signs may

be seen with NETs as opposed to SCLCs, which usually have a more rapid onset with symptoms of profound weakness, hyperpigmentation, little or no weight gain and an absence of overt Cushingoid features, the rapidity of onset and the severity of the syndrome have been both implicated as the cause of the more frequent presence of skin pigmentation and ankle oedema in SCLCs compared to other causes of ECS [7]. On the other hand, in ECS psychiatric disorders are more prominent in NETs than with SCLCs [7, 19].

It is obvious that the similarity of different types of CS mandate the necessity for a specific step-by-step diagnostic workup to resolve any diagnostic dilemma [1]. The rationale for the diagnostic confirmation of CS is to identify the loss of the specific mechanisms controlling the tightly-controlled hypothalamo-pituitary-adrenal (HPA) axis. In normal states, the HPA axis regulates cortisol secretion from the adrenal gland under the stimulus of ACTH from the pituitary, which in turn is secreted in response to CRH and vasopressin from the hypothalamus. Cortisol then exerts negative feedback control on both CRH and vasopressin in the hypothalamus, and ACTH in the pituitary. Cortisol is also secreted in a circadian rhythm; levels fall during the day from a peak at 07.00–08.00 h to a nadir at around midnight: they then begin to rise again at 02.00 h. In hypercortisolaemic states, the normal cortisol feedback mechanism of the HPA axis is distorted with loss of the normal suppression to the exogenous administration of glucocorticoids, the circadian rhythm is lost, and cortisol production increases [16]. These considerations were in part the stimulus for the Endocrine Society to recently publish a clinical practice guideline for the diagnosis of CS [15]. Hypercortisolaemia must be established before any attempt at differential diagnosis, and this is a critical step since it is related to the number of the patients that will unnecessarily be involved in laborious and costly tests, or that will be misdiagnosed as being considered inappropriately healthy but yet suffering from the long-term consequences of the sustained hypercortisolism [20]. Hence, the initial biochemical tests should ideally have maximal sensitivity rather than specificity in order to identify individuals with the mild forms of this rare disease; later, more specific tests are used to exclude false positives. This is best performed by a combination of the following tests: 24-h urinary free cortisol (UFC; at least 2 measurements) as marker of increased synthesis of cortisol exceeding the binding capacity of corticosteroid binding globulin (CBG), low-dose dexamethasone suppression (LDDST, 0.5 mg every 6 h for 2 days) or 1-mg overnight dexamethasone suppression testing (1-DST) as marker of resistance of the HPA

axis to glucocorticoid feedback and assessment of midnight serum cortisol (MNC) or late-night salivary cortisol (NSaC) as markers of the loss of circadian rhythmicity [15, 21, 22].

*These tests may not be needed when a florid and severe disease is present with massively elevated serum cortisol at any time, or a urinary Cortisol more than 4× the upper limit of normal.* In individuals with normal results in the initial investigation but with strong suspicion or when progression is documented, or when only one of test results is abnormal and clinical suspicion is low, further evaluation at a later stage is crucial to confirm or exclude the diagnosis [22]. It has been suggested that in these particularly difficult cases a dexamethasone-CRH test is mandated, but not all CS experts agree on its superiority over and above the standard LDDST [15]. Diagnostic tests based on a failure of feedback regulation were originally designed for the florid rather than the mild cases we now see, and the thresholds for serum cortisol levels have inevitably changed as the assays have become more sensitive. Hence, the conventional use of the 1-DST may still be insufficiently sensitive to detect mild cases of CS, particularly in CD; UFC assessment, even with more accurate assay techniques and in the most compliant patients, has limited sensitivity, particularly in cases of mild hypercortisolism. NSaC level should be the most sensitive indicator for CS along with MNC, but the former is clearly much more practical for screening purposes to detect rapid changes in the free biologically-active cortisol concentration [21]. The salivary cortisol (SC) test may be a good substitute of serum cortisol in some test such as 1-DST, LDDST or CRH tests to differentiate CS from healthy subjects, but may not be as good to differentiate CS from PC [22]. Recently, desmopressin (DDAVP) test has been suggested as better distinguishing even mild forms of CD from PC compared to UFC, 1-DST and MNC. Overall, it is apparent from recent studies that the 3 commonly performed initial diagnostic tests for CS (NSaC, UFC and 1-DST) are complementary, and their diagnostic performance may increase by their combination [21]. In specific cases some

tests may be superior to others. In renal failure SC post-1-DST is superior to UFC [23] as is the case of patients with cyclic CD (cyCD) [24], where SC would be most convenient to be performed immediately upon the “cycling-in” of CS, or SC testing in children to differentiate CS from obesity as a “friendlier” diagnostic tool for the paediatric population [25]. In patients with mild or cyCS, any of these tests may yield normal results and be misleading. The UFC in particular, even when measured on repeated occasions, cannot always exclude CS. In our opinion, because of the high sensitivity and ease with which repeated measurements can be performed, NSaC appears to be the most useful screening test [26]. As opposed to this, NSaC and UFC have been both found of limited clinical value compared to the 1-DST in the diagnosis of mild CS such as the case of subclinical cortisol-secreting adenomas (SCSA) [27–29]. It has been suggested that one can exclude CS by UFC assessment after 3 normal collections, while values 4-fold greater than the upper limit of normal can be considered diagnostic for CS [1]. However, small increases in cortisol production at the circadian nadir may not be detected as an increase in UFC as most of the cortisol secreted during any 24-h period is generally between 04.00 and 16.00 h [30, 31] but they might have a small but significant increase in night time cortisol secretion. Hence, the recent guidelines for the diagnosis of CS suggest use of the 1-DST or MNC, rather than UFC in patients suspected of having mild CS because of an adrenal incidentaloma [15].

The second step in the diagnostic cascade is to establish the cause of CS; plasma ACTH measurement will be either very low indicating an adrenal cause causing ACTH suppression or readily detectable. A plasma ACTH  $>20$  ng/L will immediately establish ACTH-dependence, while levels below 10 ng/L will lead to the search for adrenal pathology. Values in the “grey zone” are the most challenging since patients with both CD and adrenal pathologies might have intermediate values.

*With readily detectable ACTH, then the patient either has CD or an ectopic source. Not infre-*

quently, it is difficult to differentiate between them, as both are ACTH-dependent. The rationale for the tests used is that the corticotroph tumour cells in pituitary adenomas retain some responsiveness to the negative feedback effects of glucocorticoids, while tumours ectopically secreting ACTH generally do not [1, 7, 13, 16]. A rise in cortisol and ACTH to corticotropin-releasing hormone (CRH) test (either alone or in combination with desmopressin) usually suggests CD. An ACTH increase  $>35$  % and cortisol  $>20$  % above baseline levels is considered to be a specific response for CD when ovine-CRH is used [32], and  $>105$  % and  $>14$  %, respectively when human-CRH is used [33]. The CRH test has a sensitivity of 94 % for cortisol and ACTH responses, but approximately 5–17 % of patients with ECS respond to CRH administration [7, 16, 32, 33]. Using desmopressin instead of CRH, 40 % false-positive responses were observed in patients with ECS, with a reported sensitivity of 77–84 % and specificity 73–83 % [7, 16, 34, 35]. The high-dose dexamethasone suppression test (HDDST) is no longer in widespread use, but a serum cortisol suppression greater than 50 % is considered indicative of CD with sensitivity of 60–100 % and a specificity of 65–100 % [16, 18, 35]; when a cut-off for serum cortisol suppression was  $>60$  % this occurred in 3 % of patients with ECS, and when it was  $>80$  % it did not occur in any patient with EAS [16, 18, 35, 36]. The crucial next step to accurately identify a pituitary source is by direct sampling of the effluent of the pituitary by bilateral inferior petrosal sinus sampling (BIPSS) to CRH stimulation; especially as these tumours are usually microadenomas and may not be visible on magnetic resonance imaging (MRI) [1, 16]. This may be considered as the “gold standard” test unless there is a clear pituitary abnormality (macroadenoma), or if an ectopic source has been considered unlikely or the patient is too ill and requires immediate medical therapy. The criteria used to identify CD is an inferior petrosal sinus-to-peripheral ACTH ratio at baseline  $>2.0$  and a gradient  $>3.0$  following CRH (or desmopressin as a cheaper alternative) stimulation [1]. In patients with ECS, both ratios are expected  $<2.0$  but there are reports of false

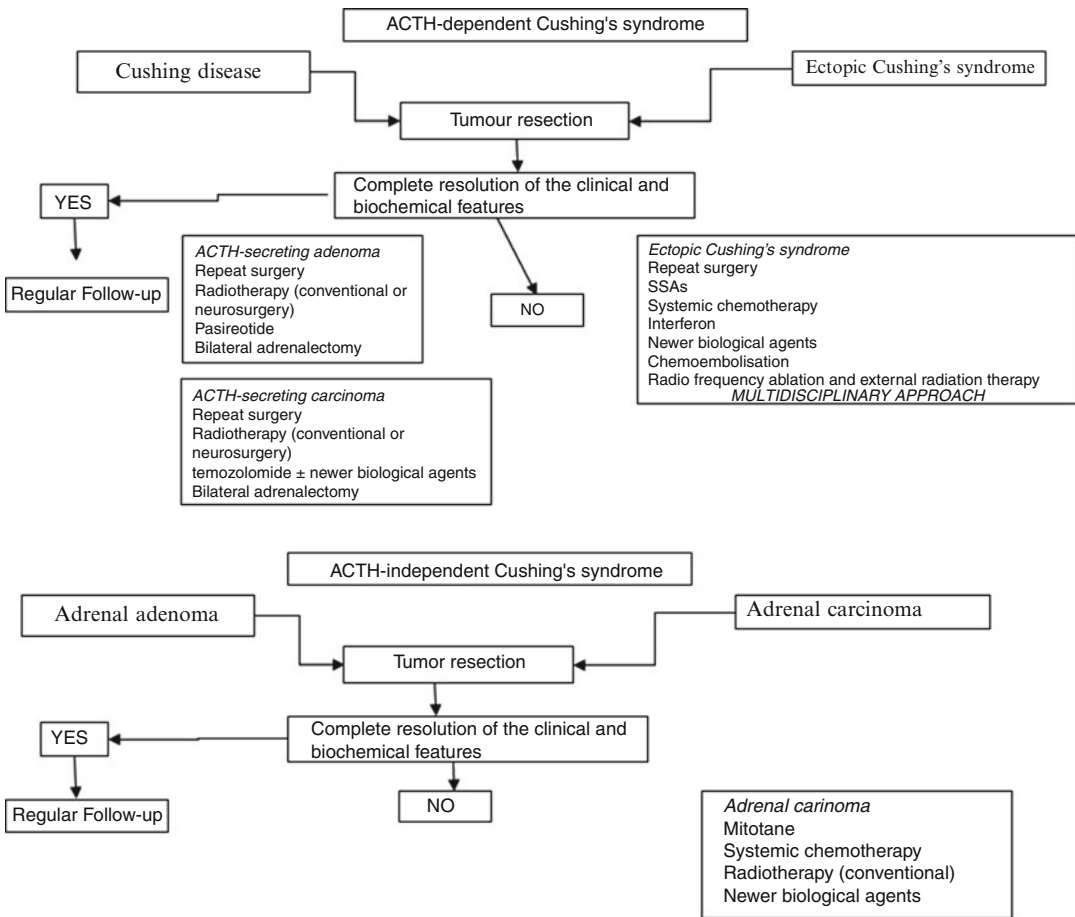
negative and false positive responses, particularly when an adequate hypercortisolaemic state is not present [7, 19, 37–41]. This test demands experience and should be performed only in specialised centres since serious complications (stroke, perforation of the arterial wall, haematoma and transitory arrhythmias) have been described [42]. As previously mentioned, ECS can also have a rapid onset and a paraneoplastic wasting syndrome which may mask hypercortisolism features; profound hypokalemia and less often hyperglycaemia may reveal its presence. Hypokalaemia is related to the degree of hypercortisolaemia since cortisol acts as mineralocorticoid because of the saturation of the enzyme 11  $\beta$ -hydroxysteroid dehydrogenase type 2. With regard to ACTH and potassium levels, no cut-off limit has been defined to distinguish patients with ECS and CD [7] since cortisol-secreting macroadenomas may share a common biochemical profile [43]. Measurement of circulating tumour markers also has a role when ECS associated with NETs is suspected. Calcitonin and gastrin have been both found to be the most commonly elevated tumour markers, regardless of tumour type [7] in ECS, while calcitonin and catecholamines need to be measured to exclude an ECS source from MTC or a pheochromocytoma, respectively. Axial imaging with thin-cut multislice-computed tomography (CT) of the chest, abdomen or with chest and pelvis MRI have the highest detection rate for ECS source identification [7, 9, 19, 44]. MRI of the abdomen is not used routinely because of the bowel movement artefact and because calcification associated with the primary tumour can more easily be identified on a CT scan; CT and MRI failure to localise the source of ECS may fall from a maximum reported 50 % to 12.5 % when an appropriate and meticulous technique is used along with a close prolonged follow-up using additional newer imaging modalities when appropriate [7]. Somatostatin receptor (SSTRs) scintigraphy may be proved helpful as ECS may be caused by small NETs expressing SSTRs adding supportive functional data to the conventional imaging techniques [7]. Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG-PET) may be proved of utility only in very occasional cases since these tumours have

usually low metabolic activity [45]. Whole-body PET with  $^{11}\text{C}$ -5-hydroxytryptophan has been proposed as universal imaging technique for NETs, in particular identifying an otherwise occult NET [46].  $^{131}\text{I}$ - and  $^{123}\text{I}$ -meta-iodobenzylguanidine scans have been also used in NET investigation [7, 9]. All these techniques may also be useful in the investigation of ECS [47]. The aforementioned modalities have resulted in only a limited use for whole-body venous catheterisation and sampling, while selective abdominal angiography and endoscopic ultrasonography may be useful in suspicion of a pancreatic NET [48] and thyroid ultrasound with fine needle aspiration may be used to exclude or diagnose MTC [49]. More sophisticated imaging techniques with limited experience such as the use of an intraoperative gamma counter in the management of metastatic ACTH-secreting bronchial carcinoids look promising [50]. The appearance of the adrenals on CT scanning may also support a diagnosis, such as the possibility of a pheochromocytoma as the ECS source; the adrenals may have normal size in 7–25 % of patients with ECS, showing moderate hyperplasia in 56 % and marked hyperplasia in 37 % compared to 50 % with either normal or mildly enlarged adrenals in CD; however, macronodular hyperplasia presents similar rates in both clinical settings [7]. *Definitive proof of an ACTH-dependent tumour requires complete resolution of the clinical and biochemical features after tumour resection or partial resolution after tumour debulking and/or demonstration of ACTH immunohistochemical staining in the tumour tissue or in metastatic deposits [1, 7].*

*On the other hand if ACTH is very low or undetectable, then the next step is imaging of the adrenals.* High-resolution CT scanning gives the best resolution of adrenal anatomy and it is accurate for masses >1 cm. A mass >5 cm in diameter should be considered to be malignant until proven otherwise [1, 7].

Less commonly, genetic testing for mutations of PRKAR1A test may be needed to confirm Carney's complex.

Summarising the more recent international consensus statements for the diagnosis and



**Fig. 9.2** Treatment algorithm in common types of Cushing's syndrome. *ACTH* adrenocorticotropin, *SSAs* somatostatin analogues

differential diagnosis of CS, published in 2008 [15] recommends that UFC ( $\geq 2$  values), LDDST, or late night salivary cortisol ( $\geq 2$  values) to be used as the first line screening tests. Abnormal results should be confirmed by an additional one of these tests. In patients with discordant results, second-line tests should be used as necessary for confirmation or they should be repeated in a second time if a suspicion of cyclicity has been raised. Once the diagnosis of CS is unequivocal, ACTH levels, CRH testing (combined with LDDST or HDDST), together with appropriate imaging, are the most useful non-invasive investigations to determine the aetiology. BIPSS

is recommended in cases of ACTH-dependent CS where the clinical, biochemical or radiological results are discordant or equivocal.

### Present and Future Therapies (Fig. 9.2)

Treatment is often complex and may require the use of surgery, radiotherapy and medical management or their combination. The specific target is to normalise cortisol levels with a reversal of clinical features. Surgical removal of the tumour causing CS is the current first-line approach for

all types of CS. Inhibitors of cortisol secretion may be required before surgery after the completion of the biochemical diagnostic workup to reverse rapidly the metabolic consequences and poor healing, or in patients who cannot be submitted to surgical procedures, or during the “waiting follow-up period” until the identification of a covert or occult tumour [48], or as alternative treatment if surgery fails [1, 16, 51]. In cases of SCLCs appropriate medical therapy is urgently instituted since prompt correction of hypercortisolism is necessary to minimise the side of myelosuppressive cytotoxic chemotherapy [7]. Compounds that target glucocorticoid synthesis (adrenal secretion inhibitors or adrenolytic drugs, such as aminoglutethimide, metyrapone, ketoconazole, etomidate, mitotane or trilostane) or function (mifepristone) have been broadly used [52]. Metyrapone and ketoconazole (either alone or in combination) are the most frequently used drugs, and appear to be more effective and better tolerated than other adrenal inhibitors. Metyrapone is rapid in onset and highly effective but the presence of hirsutism frequently precludes its use in females; ketoconazole can be used additionally or in place of metyrapone, although its onset of action is rather slower, occurring over several days while gynaecomastia or hypogonadism complicates its use in men. Intravenous etomidate at sub-anaesthetic doses remains an important option when intravenous administration is required for rapid treatment of severely ill patients and is almost always very effective; however, it should usually be used in an intensive care unit in the first instance, while fluconazole use needs to be further evaluated. Finally, if all else fails, the glucocorticoid antagonist mifepristone can reduce the symptoms and signs of CS but serum cortisol cannot be used as marker of efficacy and the patient can become Addisonian unless care is taken [53]; severe hypokalaemia may be induced (treatable with spironolactone) and further evaluation of its safety and follow-up methodologies is needed. Mitotane might be an alternative but the difficulty in monitoring and the adverse effects determine that its use be confined to the minority of patients who are intolerant or not responsive to the previous treatments, and who are unsuitable for adrenalectomy [51]. It

is equally important to manage the metabolic problems associated with florid CS. Diabetes needs to be controlled mostly with oral antidiabetics but possibly requiring insulin if severe hyperglycaemia. Present Blood pressure may also be controlled by drug therapy; hypokalaemia, which is seen in almost all patients with ECS and some 10 % of patients with other aetiologies, may be treated by spironolactone or triamterene. The high pro-thrombotic state of patients with CS may be treated by prophylactic doses of heparin. Haloperidol may be used to calm the patient with psychosis and more recently olanzepine has been also used. The hypercortisoloma patients with ECS are at high risk of sepsis, often with minimal clinical signs, and any such infection bacterial, fungal or viral must be vigorously treated properly as is seen in other immunosuppressed patients along with the management of hypercortisoloma.

Regarding CD, currently, there is no effective medical therapy that directly and reliably targets the ACTH-secreting pituitary adenoma. Various compounds with neuromodulatory properties have been used to suppress ACTH secretion in patients with CD [51], including gamma-aminobutyric acid (GABA) and serotonin antagonists, but none was proved to be of clinical value. Nuclear hormone receptor ligands involved in hypothalamo-pituitary regulation have been tested; thiazolidinediones were proved to have no effect on pharmaceutical doses used in clinical practice; retinoic acid seems to be of clinical interest since it inhibits ACTH-secretion and cell proliferation both in vitro in ACTH-producing tumour cell lines, and cultured human corticotroph adenomas, and in vivo in nude mice [54]; a very recent clinical trial showed some activity. Only dopamine agonists and somatostatin analogues (SSAs) have shown some promising results. Pasireotide targeting mostly the SSTR5 (but not octreotide and lanreotide targeting the SSTR2) and the dopamine agonist cabergoline both show therapeutic promise in CD. The recent 12-month phase 3 published study of pasireotide showed remission of hypercortisoloma, as measured by UFC, in 15 % of patients treated by 600 µg twice daily dose, and 26 % of patients on the 900 µg twice daily dose; by increasing the

daily dose with an additional 300 µg twice daily, they improved to 16 % and 29 %, respectively [55]. The major side effect was an early rise of blood glucose and glycated haemoglobin followed by stabilisation and the need of a glucose-lowering medication in 46 % of patients [55]. No other medical therapies seem to be reliably effective currently in CD [56]. However, in some ECS cases, SSTRs as well as dopamine receptors have been identified in the primary tumours, and thus their agonists, alone or in combination, have been tried as drug therapy alone or in combination with inhibitors of steroidogenesis in cases of recurrence, incomplete resection or occult tumours [7]. These combinations may also be useful in resistant CD [56].

Selective adenectomy performed by transsphenoidal surgery (TSS) remains the optimal treatment for ACTH-secreting pituitary adenomas. Remission rates range between 60 % and 80 % with a recurrence rate of 10–25 % after prolonged follow-up [57]; those rates are lower and higher respectively in patients harbouring macroadenomas. Persistent disease might mandate immediate reoperation but this appears to result in remission in only around 50 % of cases, and with a high risk of hypopituitarism [58]. When the tumour is apparent at transsphenoidal exploration, a selective adenectomy is performed, but when no tumour is obvious a hemihypophysectomy as guided by the BIPSS or MRI imaging results is often the best course of action [59]. Postoperative concentration of cortisol <50 nmol/L defines cure but is not predictive of permanent cure; this needs glucocorticoid replacement treatment until recovery of the HPA axis, i.e., when the morning cortisol levels or the cortisol response to an ACTH stimulation test is normal. Higher postoperative cortisol levels are more likely to be associated with failed surgery; however, cortisol levels may sometimes gradually decline over 4–6 weeks reflecting either gradual infarction of remnant tumour or some degree of adrenal semiautonomy [60].

After surgical failure, patients with cavernous sinus or dural invasion identified at the initial procedure should receive radiation therapy. Conventional fractionated external beam radio-

therapy achieves control of hypercortisolaemia in 50–60 % of patients within 3–5 years but with the risk of long-term hypopituitarism; this treatment seems more effective in children. Stereotactic radiosurgery may also be used if there is a clear target but with higher that initially thought relapse rates [49]. Radiosurgery is not suitable for large lesions near the optic chiasm or optic nerves. Gamma knife radiosurgery is the most popular technique achieving biochemical remission in about 55 % [61] while it can be used as salvage therapy in difficult tumours [62]. Radiosurgery using proton beams has similar efficacy as second line therapy [63]. Linear accelerator radiotherapy for CD has been reported of some success in or small numbers of patients [64]. As with all the forms of radiotherapy, new hormone deficiencies are the major drawback and the appropriate replacement regimen has to promptly be initiated. On the other hand, TSS failure should prompt re-evaluation of the diagnosis of CD, especially if previous diagnostic test results were indeterminate or conflicting, or if no tumour was found on pathological examination. When surgical therapy fails and severe symptoms of CS persist, or when drugs are not effective or tolerated and the rapid control of hypercortisolaemia is crucial, bilateral adrenalectomy is commonly performed. This option induces a rapid resolution of the clinical features but patients will need lifelong treatment with glucocorticoids and mineralocorticoids along with careful education and meticulous evaluation in their follow-up visits. A major concern in patients with CD is the development of a locally aggressive pituitary tumour, Nelson's syndrome, seen in 8–29 %, which in turn might be treated with further surgery or radiotherapy to reduce tumour size, and ameliorate hyperpigmentation [65]. Pituitary radiotherapy at the time of adrenalectomy has been considered to reduce the risk of the syndrome, but this is unproven [7, 14, 48]. Close monitoring with regular MRI scans and plasma ACTH levels should be undertaken 3–6 months after bilateral adrenalectomy and then at regular intervals thereafter. A high plasma ACTH level (>1,000 ng/l) in the year after surgery may be a predictive factor for tumour progression [1, 14].



Temozolomide is an oral alkylating precursor of dacarbazine a DNA repair inhibitor showing some results in selected aggressive corticotroph pituitary carcinomas [66]. Temozolomide response in pituitary tumours may be predicted by low expression of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase (MGMT) [67] but in practice the therapeutic response is best determined after three cycles of chemotherapy.

Resection of the causative tumour is the optimum treatment for ectopic CS; curative resection with complete remission was found to be 83 % with a single primary lesion, but overall, curative surgery was successful in only 30–47 % [9, 19]. Unilateral or complete bilateral adrenalectomy is performed in 30–56 % of patients with ECS when hypercortisolaemia cannot be treated by other means, when medical treatment was ineffective, not well tolerated, or rejected by the patient, in young women desiring pregnancy, or when a source of ECS remains occult [7, 9, 19, 42]. A multidisciplinary, individualised approach is needed in metastatic or occult disease, followed by SSAs, systemic chemotherapy, interferon, newer biological agents, chemoembolisation, radiofrequency ablation and external radiation therapy used alone or in combination [3] to control tumour growth and symptoms associated with ECS. External radiotherapy directed to the mediastinum has been used for carcinoids directed to the tumour bed or to metastatic deposits [9, 19]. Radiofrequency ablation has been also used to treat hepatic metastases of NETs, and intraoperative “octreoscanning” with a hand-held gamma detector probe has been proposed to increase the intraoperative detection rate [50]. Chemotherapy with 5-fluorouracil, streptozotocin, cisplatin, etoposide and/or adriamycin has also been used in metastatic NETs and SCLCs [19]. Hormone analogues and/or radionuclide treatment, chemoembolisation and <sup>131</sup>I-MIBG treatment have also been used [9]. No “gold standard” therapy has been approved when surgical and classical medical therapies have failed. In the context of ectopic CS, despite detailed investigation the cause of excess and unregulated ACTH production remains occult in 5–15 % of patients,

and these patients need meticulous follow-up for identification of the primary tumour [7].

Adrenalectomy is either unilateral when associated to adrenal adenoma or carcinoma, or bilateral in cases of bilateral hyperplasia or adenomas. In adrenal adenomas cure following surgery in skilled hands approaches 100 %, and is associated with low morbidity and mortality [68]. Laparoscopic adrenal removal has been shown in experienced hands to be a safe procedure and in many centres has become the approach of choice for non-malignant disease [69]. Prognosis after removal of an adenoma is good. Surgical removal of an adrenal carcinoma can be attempted with limited lesions, but when metastatic these tumours are not very radio- or chemosensitive; aggressive surgical approaches probably account for the increase in life span reported in this disease [70]. Mitotane is thought to be effective adjuvant therapy [1]. Combination chemotherapy that has been more recently investigated includes etoposide, doxorubicin and cisplatin or streptozotocin [71]. Newer biological agents are under investigation; recent studies emphasise how the metabolism of many agents can be affected by preceding mitotane [72, 73].

Finally, in AIMAH the cortisol secretion is controlled by blocking the corresponding aberrantly-expressed receptor (propranolol for beta-adrenergic receptor, somatostatin analogues for gastric inhibitory peptide receptor, leuprolide for luteinising hormone) [3].

All treated patients should be advised for the glucocorticoid withdrawal symptoms (skin flaking, fatigue, nausea, joint aches). Hypocortisolism has to be managed appropriately with glucocorticoid replacement therapy until the axis recovers, if adrenals are preserved while careful advice and instructions have to be given both orally and written to all patients.

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## Conclusions

Untreated hypercortisolaemia is associated with excess mortality and increased morbidity, and therefore rapid and life-long control is vital. The aim of the follow-up is to restore a 24-h production rate of cortisol within the normal range, even when

circadian rhythmicity has not been restored [16]. An individualised follow-up should be tailored to each patient with CS in relation to the cause and the success of the first-line treatment.

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### Clinical Recognition

Adrenal insufficiency results from the failure of corticosteroid hormone secretion either due to adrenocortical disease (primary) or secondary to the lack of ACTH secretion from the pituitary (secondary) and/or CRH secretion from the hypothalamus (tertiary). The presentation can be acute or insidious depending on the underlying cause of the adrenal gland dysfunction. Adrenal crisis is a common presentation in primary disease, but is less common in secondary or tertiary adrenal insufficiency [1].

### Presentation of Adrenal Insufficiency

1. Severe acute adrenal insufficiency or adrenal crisis
  - Hypotension and shock (>90 %)
  - Abdominal, flank, back, or lower chest pain (86 %)
  - Fever (66 %)
  - Anorexia, nausea, or vomiting (47 %)
2. Non-acute or insidious presentation
  - Neuropsychiatric symptoms such as confusion or disorientation (42 %)
  - Abdominal rigidity or rebound tenderness (22 %)
  - Hypoglycaemia (rare in adults, common in children)
  - Sudden severe headache, loss of vision or visual field defect (pituitary apoplexy)
  - Chronic malaise
  - Lassitude
  - Fatigue
  - Generalised weakness
  - Anorexia
  - Weight loss
  - Nausea and vomiting, abdominal pain, diarrhoea
  - Hyperpigmentation (only in primary adrenal insufficiency, noted in sun-exposed or pressure areas, scars after adrenal insufficiency, buccal mucosa, palmar creases)
  - Dizziness and postural hypotension
  - Improved blood pressure control in hypertensive patient
  - Salt craving (22 %)
  - Psychiatric manifestations
  - Vitiligo (as a marker of autoimmune disease)
  - Reduced axillary and pubic hair and reduced libido in females (DHEA deficiency)
  - Amenorrhoea (in 25 % due to chronic illness, weight loss or associated premature ovarian failure)

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- Features of other associated endocrinopathies (autoimmune polyglandular syndrome)
- Headache, visual field defects and other features of pituitary hormone deficiency (secondary or tertiary adrenal insufficiency)

### Biochemical Findings in Adrenal Insufficiency

- Hyponatraemia, 85–90 % (due to mineralocorticoid deficiency in primary adrenal insufficiency and dilutional in secondary adrenal insufficiency)
- Hyperkalaemia, 60–65 %, (due to mineralocorticoid deficiency)
- Elevated blood urea
- Low blood bicarbonate (metabolic acidosis in primary adrenal insufficiency)
- Elevated TSH with normal or low normal T4
- Elevated ESR
- Mild anaemia (normocytic normochromic)
- Eosinophilia
- Mild hypercalcaemia (uncommon)

### Pathophysiology

In primary adrenal insufficiency, all three layers of the adrenal cortex are affected by the disease process resulting in inadequate glucocorticoid, mineralocorticoid and androgen production; this leads to partial adrenal insufficiency, manifested by inadequate cortisol response during stress, followed by a complete insufficiency [2]. However, acute insufficiency may occur due to adrenal haemorrhage or infarction. The clinical features appear following 90 % destruction of the adrenal glands. Combined glucocorticoid and mineralocorticoid deficiency lead to increased urinary sodium loss and hypovolaemia resulting in hypotension and electrolyte imbalance (hyponatraemia and hyperkalaemia). In addition, inappropriate anti-diuretic hormone release and action on the renal tubule due to glucocorticoid deficiency contributes to the hyponatraemia. The lack of glucocorticoid negative feedback increases the release of ACTH and other POMC-peptides; it is

the  $\beta$ -MSH sequence within ACTH which is responsible for the hyperpigmentation by acting on the MSH (MCR1) receptors in the skin [3].

Mineralocorticoid deficiency is not seen in secondary adrenal insufficiency, as mineralocorticoids are principally regulated by the plasma renin–angiotensin system. Hypotension in secondary adrenal insufficiency occurs due to decreased vascular tone as a result of reduced vascular responsiveness to angiotensin II and noradrenaline. ACTH and POMC secretion are reduced and, unlike primary adrenal insufficiency, hyperpigmentation is not a feature of secondary adrenal insufficiency [4] (Table 10.1).

### Diagnostic Tests (Tables 10.2 and 10.3)

In the first instance, adrenal insufficiency needs to be confirmed with dynamic tests unless there is an Addisonian crisis. The next step is differentiation of primary from secondary adrenal insufficiency by measuring the level of ACTH. Once the primary or secondary diagnosis has been established, further investigations, e.g. imaging, auto-antibodies or microbiological screening, should be arranged to identify the underlying cause of the adrenal insufficiency. There is no need to wait for the biochemical confirmation in an adrenal crisis; treatment should be initiated without any delay as soon as suspected clinically but a blood sample taken at this time for cortisol and if possible ACTH is extremely helpful [7].

### Investigations to Establish the Underlying Cause of Adrenal Insufficiency

- Adrenal autoantibodies (21-hydroxylase auto-antibody present in 80 %, side-chain-cleavage enzyme and 17-hydroxylase)—autoimmune primary adrenal insufficiency
- Microbial and serological tests—tuberculosis, other infective cause [8, 9]
- CT adrenals and MRI adrenals

**Table 10.1** Aetiology

## Causes of primary adrenal insufficiency

- Acute or insidious presentation
  - Autoimmune adrenal insufficiency or Addison’s disease (70 % in developed countries)
  - Autoimmune polyglandular syndrome
  - Metastatic deposits from lung, breast, kidney, etc.
  - Lymphoma
  - Tuberculosis (common developing countries)
  - Histoplasmosis, cryptococcosis
  - HIV (up to 5 % patients with AIDS)
  - Infarction (anti-phospholipid syndrome)
  - Adrenoleukodystrophy (inherited disorder of long chain fatty acid metabolism, presents in childhood, may progress to severe neurological problems and possibly dementia)
  - Congenital adrenal hyperplasia
  - Congenital adrenal hypoplasia (mutation/deletion of DAX 1/SF 1 genes)
  - Familial glucocorticoid deficiency (various mutations, mineralocorticoids usually spared)
  - Adrenalectomy
  - Drugs (ketoconazole, fluconazole, phenytoin, rifampicin, etomidate, aminoglutethimide)
- Acute presentation [5, 6]
  - Haemorrhage (trauma, anticoagulants)
  - Waterhouse–Friderichsen syndrome (meningococcal septicaemia)

## Causes of secondary and tertiary adrenal insufficiency

- Withdrawal of exogenous glucocorticoid, very common (suppression of the hypothalamo-pituitary-adrenal axis, abrupt withdrawal can cause adrenal crisis)
- Pituitary tumours
- Pituitary apoplexy (acute presentation)
- Pituitary surgery
- Pituitary radiotherapy
- Treated Cushing’s disease
- Tuberculosis, sarcoidosis, langerhans cell histiocytosis, haemochromatosis, lymphocytic hypophysitis
- Isolated ACTH deficiency (rare)
- Trauma to the pituitary
  - Large adrenals with or without calcification seen in tuberculosis and metastatic deposits
  - Small atrophic glands in autoimmune primary adrenal insufficiency, but can also be seen in chronic secondary adrenal insufficiency
  - Adrenal haemorrhage and adrenal vein thrombosis (MRI better than CT)

- MRI pituitary and hypothalamus—secondary or tertiary adrenal insufficiency
- Biopsy of adrenal or pituitary—occasionally
- Very long chain fatty acid-adrenoleukodystrophy
- 17-OH progesterone and 24 h urine steroid profile (classic CAH, in neonates)
- Other autoimmune markers and hormonal assays to assess autoimmune polyglandular syndrome
  - Thyroid function (autoimmune hypothyroidism)
  - Plasma glucose (diabetes mellitus type 1)
  - Serum calcium and PTH (autoimmune hypoparathyroidism)
  - Anti-parietal cell antibody, intrinsic factor antibody (pernicious anaemia)
  - Endomyseal antibody or tissue transglutaminase (coeliac disease)
  - Liver function tests (autoimmune hepatitis)

**Other Investigations**

- Plasma renin activity, high in primary adrenal insufficiency due to mineralocorticoid deficiency
- DHEAS (low in women)

**Differential Diagnosis**

Many of the changes seen in adrenal insufficiency are non-specific, and it overlaps with mild depression, chronic fatigue syndrome, and generalised malignancy or sepsis, especially slow-onset infections such as TB. One of the most useful discriminants for Addison’s disease is the presence of hyperpigmentation [10], which should always be sought. For secondary and tertiary adrenal failure, the critical features related to other possible pituitary defects such as gonadotrophin deficiency, headache and visual failure. However, it should be noted that ACTH deficiency is generally a feature of advanced pituitary failure other than in lymphocytic hypophysitis, when it may occur early or as an isolated endocrine feature.

**Table 10.2** Investigations to confirm adrenal insufficiency

Tests	Procedure	Interpretation of the result	Comments
Short Synacthen test (SST)	Take blood sample for 9 a.m. cortisol and 9 a.m. ACTH level Administer 250 mcg Synacthen/ Tetracosactrin (ACTH) i.m. or i.v. 30 min later collect blood sample for serum cortisol level	Serum cortisol response <450 nmol/L at 30 min confirms adrenal insufficiency	Different criteria may apply according to cortisol assay Recent onset secondary adrenal failure may produce a normal response SST can be done at any time of the day Oestrogens can give falsely high cortisol levels by elevating cortisol- binding globulin; discontinue oestrogen at least for 6 weeks prior to the SST If already on glucocorticoid replacement, omit steroid dose before the test, except dexamethasone For hydrocortisone or prednisolone hold off evening and morning dose
Insulin tolerance test	Overnight fast state, insert cannula, take venous blood for basal glucose and cortisol, administer iv soluble insulin 0.15 units/kg, collect venous blood at 30, 45,60,90, and 120 min for glucose and cortisol Repeat insulin dose if glucose does not fall <2.2 mmol/L at 45 min	Fall of glucose <2.2 mmol/L with corresponding failure of cortisol response >450 nmol/L confirms adrenal insufficiency (but depends on cortisol assay)	Contraindications <ul style="list-style-type: none"> <li>• Basal cortisol &lt;100 nmol/L</li> <li>• Untreated hypothyroidism</li> <li>• Abnormal ECG</li> <li>• Ischaemic heart disease</li> <li>• Seizure history</li> <li>• Craniotomy</li> <li>• Age &gt;70</li> </ul> “Gold standard test” Sensitive test for recent onset secondary adrenal insufficiency Discontinue oestrogen at least for 6 weeks prior to the test
9 a.m. cortisol level	Collect serum cortisol level at 9 a.m.	9 a.m. cortisol <100 nmol/L suggests adrenal insufficiency	Can be useful in recent onset secondary adrenal insufficiency (2 weeks) In severe stress such as sepsis a “normal” level may still indicate adrenal insufficiency
Random cortisol	Collect random serum cortisol level if adrenal insufficiency is suspected, prior to steroid replacement	Undetectable level suggests adrenal insufficiency	Not very reliable, unless very low

## Treatment

### Management of Adrenal Crisis

This is a life threatening medical emergency which requires prompt treatment with hydrocortisone and fluid replacement. Once clinically suspected, there should be no delay in initiating treatment pending biochemical confirmation. The management approach should be similar to the resuscitation of any critically ill patient.

- Maintain airway and breathing
- Establish venous access with two large bore cannulae
- Collect venous blood sample for
  - Urea and electrolytes
  - Blood urea
  - Full blood count
  - Bicarbonate
  - Infection screen
  - Random cortisol, ACTH and plasma renin



**Table 10.3** Investigations to differentiate primary from secondary adrenal insufficiency

Tests	Procedure	Interpretation of the results	Comments
9 a.m. serum ACTH level	Take venous blood sample at 9 a.m.	Elevated ACTH (>60 ng/L) confirms primary adrenal insufficiency Low ACTH level (<10 ng/L) confirms secondary or tertiary adrenal insufficiency	ACTH 10–20 ng/L can be equivocal, consider long Synacthen test
Long Synacthen test	Take blood sample for 9 a.m. cortisol and ACTH level Administer 1 mg depot Synacthen i.m. Collect blood sample for serum cortisol level at 30, 60, 120 min, 4, 8, 12 and 24 h	Progressive rise in cortisol response in secondary adrenal insufficiency Little or no response in primary adrenal insufficiency	Useful in differentiating primary from secondary adrenal insufficiency when ACTH level is equivocal

- Intravenous fluids
- 0.9 % normal saline 1–3 l within 12 h
- 0.9 % saline to be continued, guided by volume status and urine output, for 24–48 h
- But caution should be taken in correcting chronic hyponatraemia (not more than 10 mmol/L in 24 h) to prevent central pontine myelinolysis
- Dextrose infusion may be required if there is evidence of hypoglycaemia which is rare
- Steroid replacements
- I.v. bolus hydrocortisone 50–100 mg stat and then i.m. every 6 h for 24–48 h
- Note that the half-life of hydrocortisone is 90–120 min after intravenous injection, and prolonged after i.m. administration
- Switch to oral hydrocortisone with a tapering dose (usually 20–10–10 mg) after 48 h if oral intake is resumed and there is no other major illness
- Alternatively dexamethasone i.v. 4 mg stat; some recommend dexamethasone while dynamic tests are awaited, as dexamethasone does not interfere with the assay, but we prefer hydrocortisone for its mineralocorticoid activity (which is negligible in dexamethasone), because the mineralocorticoid action is effective in correcting the electrolyte imbalances; in addition, biochemical confirmation is not essential in an acute emergency setting
- There is no need for fludrocortisone replacement in an acute crisis. The mineralocorticoid

activity of hydrocortisone and 0.9 % saline infusion is sufficient to correct electrolyte imbalances

### Management of Chronic or Insidious Onset of Adrenal Insufficiency Glucocorticoid Replacements

There are various types of cortisol replacement regimens and no head-to-head comparison data are available to advocate one over the other. Clinicians can make their decision based on the form of glucocorticoid available locally and the clinical need.

- Hydrocortisone
  - Short acting, given in two to three divided doses
  - Usually given 10 mg on waking, 5 mg in the afternoon and 5 mg in the early evening
  - This approximately mimics the endogenous glucocorticoid diurnal rhythm
  - Obese individuals may require more glucocorticoid replacement than lean individuals.
  - Easy to monitor the adequacy of replacement with biochemical tests
- Cortisone acetate
  - Short acting (but longer than hydrocortisone)
  - 25–35 mg in three divided doses
  - Metabolised in liver to active form, hydrocortisone
  - No i.v. preparation

- Prednisolone:
  - 5–7.5 mg on waking
  - Long acting, once daily dose is sufficient
  - Some may need additional 2.5 mg in the evening
  - Does not mimic diurnal rhythm of endogenous cortisol
  - Better choice in non-compliant patients with multiple daily dose
  - Cross-reacts in most cortisol assays
- Dexamethasone:
  - 0.25–0.75 mg on waking
  - Inter-individual variable metabolism makes it difficult to predict the adequate dose
  - Dose needs to be increased if patient are on hepatic enzyme inducing medications

### Mineralocorticoid Replacement

- Required only in primary adrenal insufficiency
- Fludrocortisone (9- $\alpha$ -fludrocortisone) 0.05–0.2 mg daily
- May need to increase dose in hot weather with increased perspiration
- Available in oral preparation only
- If parenteral action required, use DOCA if available

### DHEA Replacement [11]

- Can be offered to women with low energy, low mood and lack of libido
- Some variable evidence of benefit
- Initially 25–50 mg daily for three to six months and continued if clinical response
- Not generally available on prescription, but can be obtained as a “health food” supplement or over the internet

## New Therapies [12]

It may be noted that slow-release hydrocortisone is becoming available in some countries, and its pharmacokinetic profile much more clearly parallels the physiological levels of cortisol. It is taken once-daily, and is thus clearly also more convenient for patients and may aid compliance. However, it is considerably more expensive than

immediate-release hydrocortisone, and it remains to be seen whether it is to become the initial treatment of choice.

### Follow-up

The aim is to ensure adequate physiological glucocorticoid and mineralocorticoid (in primary adrenal insufficiency) replacement, and to reduce the risk of adrenal crisis by providing necessary education to the patients.

The dose of steroids should be adjusted according to clinical symptoms as well as the biochemical parameters.

### Assess Glucocorticoid Replacement

- Inadequate replacement
  - Lethargy, tiredness
  - Low serum cortisol level on cortisol day curve (useful for hydrocortisone or cortisone replacement only)
- Over replacement
  - Cushingoid appearance
  - High 24 h urinary-free cortisol
  - High serum cortisol on hydrocortisone day curve (useful for hydrocortisone or cortisone replacement only)
  - Low bone mineral density

### Assess Mineralocorticoid Replacement

- inadequate replacement
  - Postural hypotension
  - High plasma renin activity (should be at the upper level of normal)
- Over-replacement
  - Hypertension
  - Oedema
  - Hypokalaemia

### Patient Education [12]

This is very crucial in the management of adrenal insufficiency. All patients with adrenal insufficiency should be educated about their condition and the emergency measures they should take at home to prevent adrenal crisis. This information should be reinforced during the annual follow-up visits

by the clinicians and, if possible, through a structured patient education programme.

- Steroid “sick day” rules
  - During any acute illness or stress the total oral glucocorticoid dose should be doubled for at least 72 h; if the patient remains unwell after 72 h, they should contact the caring physician
  - There should always be a supply of additional oral glucocorticoid on prescription for sick days
  - There is no need to increase the mineralocorticoid dose
- Steroid Emergency Pack
  - Every patient should be provided with this pack to keep at home
  - The pack contains a vial of 100 mg hydrocortisone or dexamethasone 4 mg, a syringe and a needle
  - The patient and/or any responsible family member should be educated to administer this medication intramuscularly or subcutaneously during an emergency situation, i.e. a severe accident, significant haemorrhage, fracture, unconsciousness, diarrhoea and vomiting, and they should call the emergency medical personnel immediately
  - The expiry date on the pack should be checked regularly and replaced with a new pack if expired
  - The patient should be advised to take the pack when travelling
- Medical-Alert bracelet or pendant and emergency steroid card
  - Every patient should wear or carry these in which the diagnosis and daily medication should be clearly documented

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## Introduction

Adrenal incidentalomas are, by definition, adrenal lesions discovered when radiological procedures are performed for indication other than suspected adrenal disease, as the adrenal glands are common sites for various types of lesions—benign and malignant, hormonally active or inactive [1].

Most cases of AI are due to cortical adenomas, whose prevalence in large series ranges from 70 to 90 %. Although inactive adenoma is considered the most common adrenal lesion other adrenal lesions may be functionally active, requiring hormonal investigation, along with subsequent medical and surgical treatment [2, 3] (Table 11.1).

Prevalence increases with age, especially in the 5th and 7th decades of life, but is regarded as uncommon in individuals with less than 30 years of age. Hypertension, obesity, and diabetes have been frequently reported, particularly in bilateral lesions, and this may be due to the presence of subclinical hypercortisolism [4].

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## Imaging Procedures

CT scan is the primary and preferred method used for evaluation of adrenal glands because it is a procedure that is readily available, while offering the highest spatial resolution. Contrast enhancement and deenhancement (washout) in late phases (15 min) are helpful to characterize the lesions; however, noncontrast CT is often sufficient for the diagnosis of AI (Fig. 11.1).

Among the characteristics for identification of potentially malignant lesions, the first to be observed is the size of the mass. Various cut points have been proposed ranging between 3 and 6 cm (more often 4 cm) of diameter based on the fact that primary carcinomas of the adrenal with measurements lower than these are quite rare. However, adrenal carcinomas of 2.5 cm have been documented, and the use of these cutoff limits can exclude patients harboring carcinomas that are still small, and therefore, offer the greatest likelihood of being able to be treated and cured if operated upon in early stages [5, 6].

The next, and probably the most important, aspect to be seen is related to the noncontrast attenuation of the lesion when evaluated by CT. The rationale is that adrenal adenomas, due to their high content of intracellular lipids, usually exhibit low attenuation. In this regard, using a cutoff level of 10 HU (Hounsfield units) or less, a sensitivity of 96–100 %, and a specificity of 50–100 % have been reported for diagnosing a benign lesion [1, 7]. Several authors reported

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**Table 11.1** Etiology, prevalence, and laboratory evaluation of adrenal incidentalomas

Etiology	Prevalence (%)	Laboratory screening
Nonfunctional adenoma	85	Normal
Subclinical Cushing's syndrome	7	1-mg DST (serum cortisol >3 µ/dl) Plasma ACTH (<5 pg/ml)
Pheochromocytoma	3.5	24-h urine metanephrines >2 mg/g Cr
Hyperaldosteronism	0.7	Plasma aldosterone ≥15 ng/dl with a APRR ≥20
Nonfunctional adrenocortical carcinoma	2	Normal



**Fig. 11.1** A 52-year-old woman with primary hyperparathyroidism and hypertension had a CT scan to evaluate for renal calculi. A lesion (5.5 cm) in right adrenal gland was discovered. Noncontrast attenuation: 39 HU. Contrast washout: 42 % in 15 min

high sensitivity and specificity in CT after using contrast. Percentage deenhancement, the so-called washout, of at least 60 % in 15 min has been shown to be 98 % sensitive and 92 % specific for benign lesion [7] (Fig. 11.1).

Other features of benign lesions that can be evaluated by CT, such as regular margins and homogeneous attenuation, have low accuracy and are less useful in diagnosis. Calcifications, necrosis, and hemorrhages are atypical events, but occur more specifically in larger lesions.

In adrenal hemorrhage, a clinical condition associated with sepsis, coagulation disorders, adrenal tumors (such as pheochromocytomas), and abdominal trauma, CT scan initially show high density that gradually decreases as the hematoma subsides which may in turn become a pseudocyst. Other lesions with characteristic features include cysts and myelolipomas. Endothelial cysts and pseudocysts are the most common, accounting for more than 80 % of the cases.

CT is useful in demonstrating the presence of liquid (hypodense) and generally thick capsules, whereas MRI shows hypointensity on T1, and hyperintensity on T2. Patients with adrenal cysts can, in some cases, benefit from fine needle aspiration (FNA) biopsy guided by ultrasound or CT for decompression and/or cytologic evaluation of the aspirated fluid. Since pseudocysts can originate from pheochromocytomas, measurements of serum or urinary catecholamines or metanephrines are always recommended [3, 5, 6].

Myelolipomas, in turn, are benign tumors composed of mature adipose tissue and normal hematopoietic tissue, corresponding to around 7–15 % of AI cases. They are almost always asymptomatic lesions. Seen by CT, they appear as hypo-dense lesions (–40 HU), due to the presence of fat. Calcifications and hemorrhages may also be present [5]. Bilateral lesions occur in about 20 % of AI cases and are usually due to metastases, granulomatous diseases, adrenal hemorrhage, or congenital adrenal hyperplasia. In this regard, positron emission tomography (PET) using 2-<sup>18</sup>F-fluoro-2-deoxy-D-glucose, has been used in cancer patients to evaluate the possibility of adrenal metastasis by demonstrating increased uptake, as well as being able to differentiate these cases from adenomas, which may not demonstrate the same uptake [7, 8].

### Fine Needle Aspiration (FNA)

This procedure is useful in cases where there is known malignant disease (prior or concurrent), and suspicion that the adrenal nodule is metastatic. Diagnosis of metastasis in this situation has corresponded on average to about half the cases. The incidental finding of metastatic

adrenal lesions in a patient with no clinical symptoms is considered to be rare. FNA should always be preceded by hormonal evaluation to rule out pheochromocytoma as catecholamines may be released with subsequent increase in blood pressure during the procedure. FNA should not be performed in the suspicion of adrenocortical carcinoma due to the risk of tumor seeding [6–8].

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## Hormonal Evaluation

The prevalence of autonomous adenomas that produce cortisol among cases of incidentalomas is from 5 to 20 %. This condition has been classified as subclinical Cushing's syndrome (SCCS). Diagnosis can be made by a combination of 1-mg dexamethasone suppression test and plasma ACTH concentrations. Various cutoff values for cortisol have been proposed ranging from 2 to 5 µg/dl [7, 9].

The natural history of SCCS is not completely understood. In many patients the condition does not progress but in some it may evolve to clinical Cushing's syndrome. Patients must be evaluated for the presence of arterial hypertension, obesity, and glucose intolerance. Patients who demonstrate clinical consequences attributable to cortisol excess are likely to benefit from surgery. In asymptomatic patients, conservative management is appropriate, along with clinical and laboratory monitoring.

The prevalence of primary hyperaldosteronism, as a cause of arterial hypertension in the general population, has been growing due to its increasing recognition and diagnosis, especially in normokalemic patients, through routine measurements of aldosterone, and plasma renin activity (PRA). Hypertensive patients, hypokalemic or not, demonstrating AI should be evaluated, initially with the aldosterone–plasma renin activity ratio (APRR), providing a diet with normal amount of sodium, and if possible, stopping medications such as spironolactone, diuretics, and beta blockers that may interfere with measurements [7, 8]. Plasma aldosterone values of more

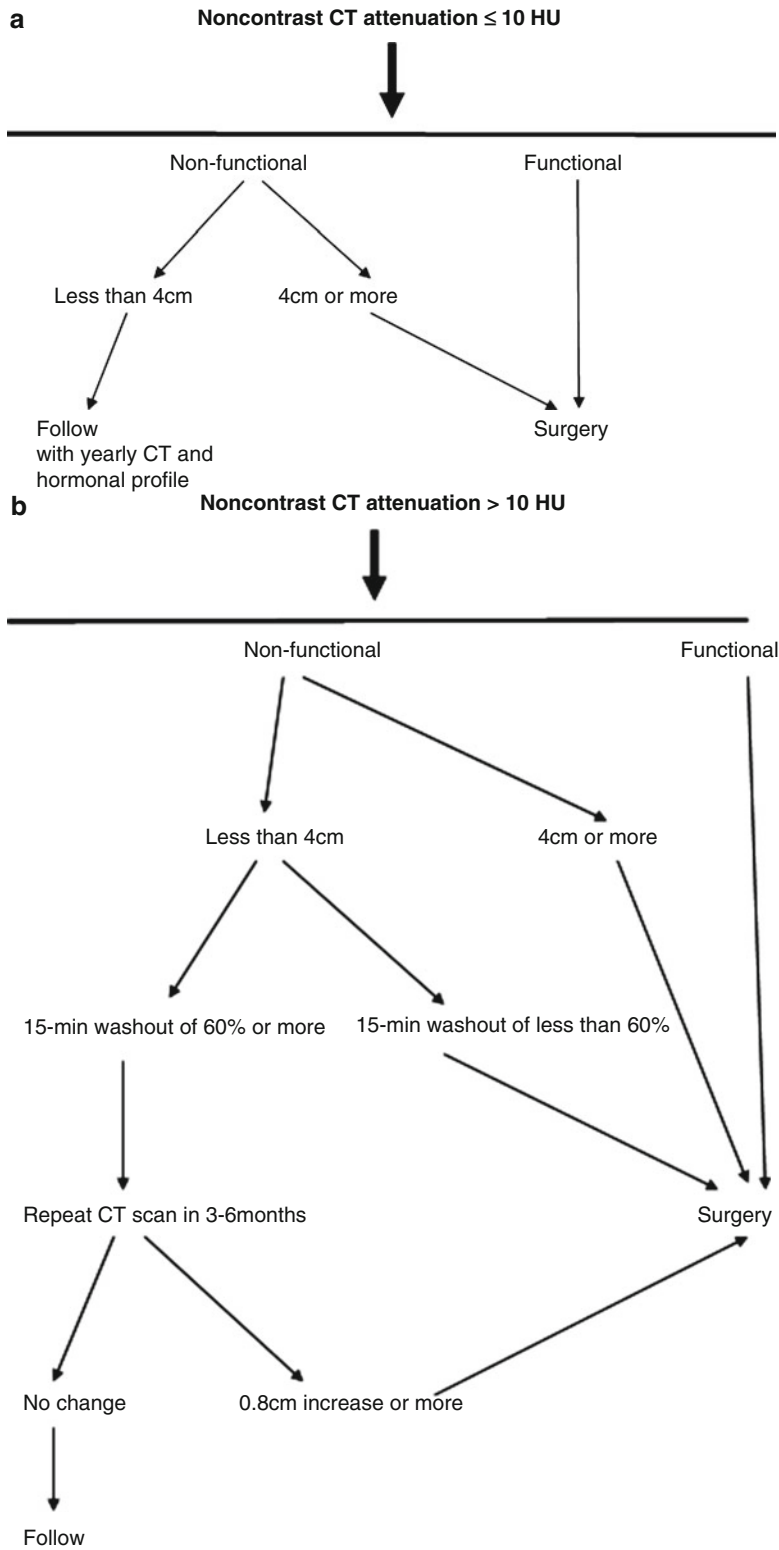
than 15 ng/dl in the presence of an APRR of 20 or more should be considered a positive screening and dynamic tests is necessary. Additional test should include aldosterone suppression test with 2 L of normal saline infusion over 4 h followed by measurement of plasma aldosterone. Oral captopril 50 mg may be given after 2 h of infusion. At the end of 4-h infusion, plasma aldosterone level above 10 ng/dl confirms the diagnosis of hyperaldosteronism.

Pheochromocytomas comprise about 10 % of AI cases. Many of these patients are asymptomatic, and half of them have arterial hypertension and adrenergic symptoms which may be paroxysmal. Metaiodobenzylguanidine scintigraphy (MIBG) has almost 100 % specificity (albeit with much lower sensitivity than MRI and CT), and can be used to confirm cases with positive hormonal screening. This should be done with measurements of plasma catecholamines or free metanephrines or urinary catecholamines and metanephrines/normetanephrines [8]. Plasma catecholamines above 2,000 pg/ml or urine norepinephrine above 100 µg/g urine creatinine/24 h, or urine epinephrine above 10 µg/g urine creatinine/24 h, or urine metanephrine above 2 mg/g urine creatinine are suggestive of the presence of pheochromocytoma. Highest specificity may be obtained with a plasma free metanephrine value above 1.4 pmol/ml [1, 2, 8].

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## Patient Follow-Up

The clinical evolution of AI patients who exhibit radiological characteristics suggesting a benign and normal hormonal profile is usually favorable. Some patients (about 20 %) progress to hormonal hyperfunction, notably clinically evident hypercortisolism, or SCCS, and more rarely pheochromocytomas. In those patients with nonfunction lesion with noncontrast attenuation less than 10 HU, a one-time follow-up CT scan in 12 months is recommended [1, 8]. Those with lesion less than 4 cm but more than 10HU should have a CT scan done in 3–6 months and then yearly for 2 years (Fig. 11.2a, b).



**Fig. 11.2** Approach to the patient with incidentally discovered adrenal mass, with low (a) and (b) attenuation

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## Treatment

Most lesions can be removed by laparoscopic surgery, including pheochromocytomas, cortisol-producing adenomas (Cushing's syndrome), aldosteronomas, nonfunctional adenomas, and more rarely, cysts or myelolipomas. Tumors larger than 10 cm in diameter should preferably be operated with conventional techniques due to the increased risk of malignancy, and the greater difficulty involved in the laparoscopic procedure [10].

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## Primary Aldosteronism

### The Renin–Angiotensin–Aldosterone System (RAAS)

The RAAS is traditionally seen as an endocrine circulating system, in which renin produced by the juxtaglomerular cells cleaves angiotensinogen to angiotensin I (Ang I). Ang I is subsequently cleaved at the endothelial level into a potent vasoconstrictor called angiotensin II (Ang II), mainly by angiotensin converting enzyme (ACE). Ang II participates in regulatory control of blood pressure and promotes inflammation, fibrosis, and remodeling [5]. Ang I might also be directly or indirectly converted to Ang 1–7, which is degraded by ACE to Ang 1–5, while Ang II is degraded to Ang III and IV by aminopeptidases. These factors act through (pro)renin receptor, Ang type 1, 2, and 4 receptors, and

Mas receptor (Fig. 12.1). This whole system has paracrine, autocrine, and intracrine activities.

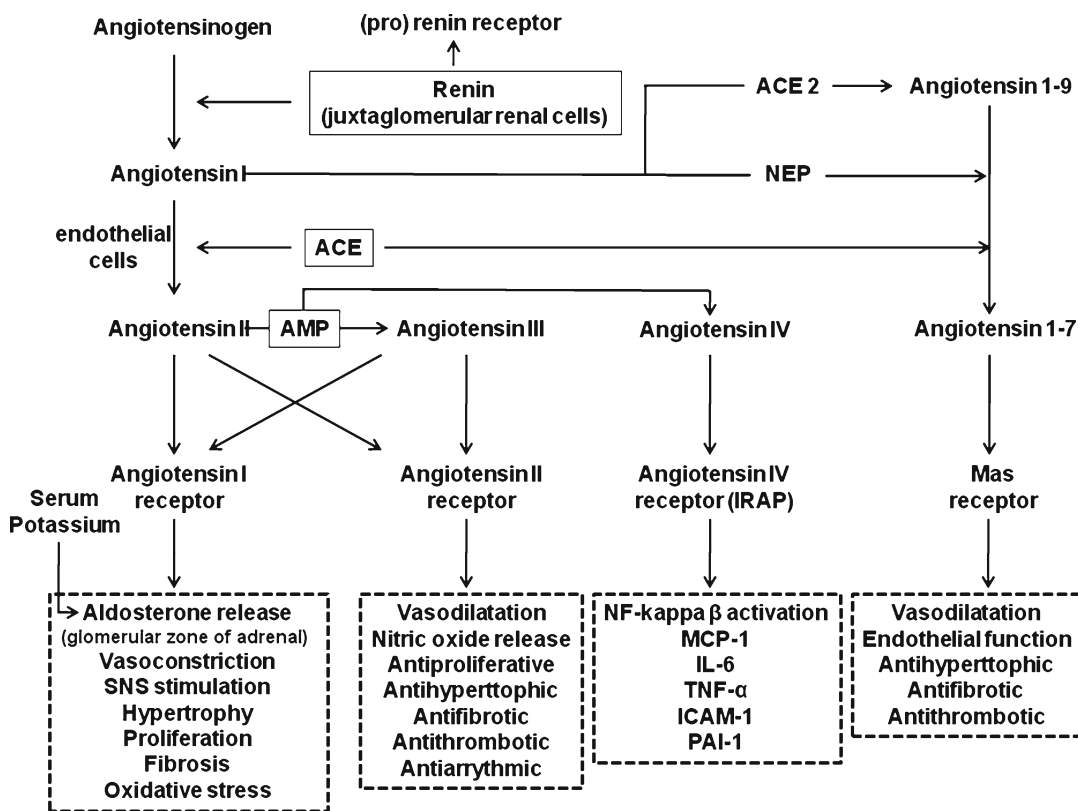
Aldosterone is synthesized mainly by the adrenal gland (glomerular zone), brain and vascular endothelium. The heart expresses steroidogenic acute regulatory proteins and aldosterone synthase. However, evidence suggests that aldosterone in the heart is derived from circulating aldosterone. Aldosterone is basically a steroid hormone produced by the adrenal cortex that contributes significantly to maintaining the body's balance of plasma sodium and fluid. The main factors responsible for aldosterone release are the plasma levels of potassium and Ang II. Low plasma levels of potassium and Ang II reduce the secretion of aldosterone, as in cases of volume expansion by excess salt intake. Aldosterone acts by binding to epithelial mineralocorticoid receptors in the kidney, essentially resulting in salt and water retention and potassium excretion. Mineralocorticoid receptors are also found in the brain, cardiomyocytes, and muscle cells of arteries. An excess of aldosterone may promote the deterioration of target organs such as the heart, kidney, and vessels—regardless of blood pressure—through perivascular inflammation that progresses to necrosis and finally diffuse fibrosis. These pro-inflammatory and pro-fibrotic effects of aldosterone have been demonstrated experimentally and in clinical studies with a higher prevalence of left ventricle hypertrophy, atrial fibrillation, microalbuminuria, chronic kidney disease, and endothelial dysfunction. The finding of metabolic syndrome

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**Fig. 12.1** The main components of the Renin-Angiotensin-Aldosterone System (RAAS) and its physiological role in the regulatory control of blood pressure, inflammation and cardiovascular function. *ACE* angiotensin converting enzyme, *NEP* neutral endopeptidase, *AMP*

aminopeptidase, *IRAP* insulin-regulated aminopeptidase, *SNS* sympathetic nervous system, *MCP-1* monocyte chemoattractant protein-1, *IL-6* interleukin-6, *TNF- $\alpha$*  tumor necrosis factor alpha, *ICAM-1* intercellular adhesion molecule-1, *PAI-1* plasminogen activator inhibitor-1

is also more frequent in patients with hyperaldosteronism than in patients with essential hypertension [6–8].

## Etiology and Prevalence

Primary aldosteronism includes a set of changes with autonomous overproduction of aldosterone that is not dependent on the normal functioning of the RAAS and is suppressed by excess of salt. The most common causes are adrenal adenoma, unilateral or bilateral adrenal hyperplasia, or more rarely, glucocorticoid-remediable hypertension (GRA).

It is believed that 10 % of all hypertensive patients have primary aldosteronism, which is now considered the most common cause of secondary

hypertension. It is noteworthy that, among patients with resistant hypertension, 20 % have primary aldosteronism. According to the classification of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), it is estimated that primary aldosteronism is found in 2 % of stage 1 hypertensive patients, 8 % of stage 2, and 13 % of stage 3 [9].

## Diagnostic Approach

The diagnosis of primary aldosteronism is very important, because these patients show higher cardiovascular morbidity and mortality than patients of similar age, gender, and degree of blood pressure. Primary aldosteronism should be

suspected in patients with stage 2 or 3 of hypertension or resistant hypertension (defined by the failure to reach goal blood pressure in patients adhering to full doses of an appropriate 3-drug regimen that includes diuretics), in hypertensive patients who have hypokalemia or hypokalemia induced by diuretics, in patients who have an adrenal incidentaloma, in hypertensive patients with a family history of early-onset hypertension or with stroke under the age of 40 years, and in all hypertensive patients who have a first degree relative with primary aldosteronism [4, 9–12].

In suspected cases, it is recommended that the clinician use a screening tool to differentiate between primary aldosteronism and secondary hyperaldosteronism due to excessive production of aldosterone that does not depend on hyperactivity of the RAAS. The most common test is the ratio of the plasma aldosterone concentration and plasma renin activity (ARR) [13]. Measurements should be made in the morning in an outpatient setting, with the individuals at least 2 h out of bed, at sitting or standing position for at least 15 min. There should be no limitation on the intake salt, and the physician should be aware of different antihypertensive drugs that can affect the results. In cases where antihypertensive medication is suspended for performing the test, it is recommended a close monitoring of blood pressure. If present, hypokalemia needs to be corrected, because it is a confounding factor in the interpretation of the test. After the plasma potassium is corrected, an interval of 4–6 weeks before performing the ARR should be observed. Care and specific recommendations for the collection and interpretation of the results have been recently compiled [11, 12]. Values that suggest primary aldosteronism are those greater than 30, considering the plasma aldosterone in ng/dl, and plasma renin activity in ng/ml/h. The higher the ARR, the greater the likelihood of primary aldosteronism [13].

After an altered screening test, it is necessary to perform a confirmatory test due to the high rate of false positive results, methodological variability and inappropriate sample collection. Confirmatory tests require the demonstration of no suppression of aldosterone production with expansion of

plasma volume and/or blockade of the RAAS using an inhibitor of ACE. One of such tests is the high salt diet for 3–4 days; the diet causes a urinary sodium excretion  $>200$  mEq/24 h and a decrease in urinary aldosterone excretion to 12–14  $\mu\text{g}/24$  h. The patient's blood pressure should be monitored, as the patient undergoes this test in an outpatient setting. Patients with resistant hypertension, heart failure, and chronic kidney disease should not perform this confirmatory exam. Another possibility is an inpatient-based test that involves an overload of salt and water with an infusion of 2 l of normal saline over 4 h and observing whether suppression of plasma aldosterone to 5–10 ng/dl occurs. The combined use of a high salt diet for 3–4 days with the administration of fludrocortisone 0.1 mg orally every 6 h causes an extremely high retention of liquid, and there is a suppression of plasma aldosterone to levels of 5–6 ng/dl. This confirmatory test needs to be done at a hospital, because there is a significant chance of edema and potassium loss. Finally, the use of captopril 25 mg (with measurement of plasma aldosterone 2 h later) can suppress the aldosterone to values lower than 12 ng/dl [4, 9–12].

Patients with a positive confirmatory test should undergo a computed tomography (CT) scan with 2–3 mm slices or a magnetic resonance imaging (MRI) of the adrenal glands. In particular, imaging helps to identify large masses ( $\geq 4$  cm) that can be excised and those with higher risk of malignancy. It also may be useful to visualize the anatomy for an adrenal venous sampling. However, the sensitivity and specificity of CT/MRI are low when used without a confirmatory test in advance, since adrenal imaging might fail to detect many small adenomas, and yet may demonstrate non-functioning nodules in the contralateral gland and apparently unilateral lesions in patients with bilateral adrenal hyperplasia. If only imaging is used, agreement with direct measurement from the adrenal veins only occurs in about 50 % of the cases. Hence, the isolated use of the imaging to define surgical therapeutic approaches leads to inadequate treatment in nearly half of the patients [4].

As a general rule, patients with a screening, confirmatory, and imaging test suggestive of primary aldosteronism should undergo a selective cannulation of the adrenal vein for measurement of aldosterone and cortisol. Nevertheless, this is an invasive procedure that requires a careful patient preparation, a defined protocol, an experienced interventional radiologist, and an accurate data interpretation. Right adrenal vein cannulation is more difficult, due to its smaller caliber and its flow directed to the inferior vena cava rather than the renal vein. The main purpose is to distinguish between unilateral and bilateral disease, detecting a unilateral overproduction of aldosterone that could possibly benefit from adrenalectomy. The relationship should be 3:1, 4:1, or greater for lateralization to be considered positive. The ratio between aldosterone and cortisol can be used to confirm lateralization, and in this case it should be greater than 2:1. In some centers, cosyntropin has been used in bolus or continuously to improve the sensitivity of the method. In reference centers, the sensitivity and specificity of this procedure to detect an unilateral overproduction of aldosterone is 95 and 100 %, respectively [4, 9–12].

In cases of selective cannulation failure of the adrenal vein for measurement of aldosterone and cortisol, the options are to repeat the procedure another time, to treat the patient with mineralocorticoid receptor antagonists or to consider surgical treatment guided by other tests and clinical findings. There are other tests with lower sensitivity and specificity, such as postural stimulation tests, scintigraphy with iodocholesterol, and the dosage of 18-hydroxycorticosterone [11].

## Genetic and Molecular Basis

The understanding of the genetic and molecular basis of primary aldosteronism has quickly evolved. Three variants of familial hyperaldosteronism are known today [14]. Early onset of hypertension and severe target organ damage are hallmarks of the inheritable forms. The underlying gene defect has already been identified in

familial hyperaldosteronism type I, with ongoing research for types II and III. A highly variable phenotype often precludes the discovery of the familial appearance of these syndromes, making the family history extremely important to discover some Mendelian pattern of inheritance. The identification of affected families is highly rewarding because all variants can potentially be cured or at least specifically treated. Testing the relatives of an index patient may sometimes allow the start of a preemptive treatment.

Familial hyperaldosteronism type I, also known as GRA, is an autosomal dominant disorder caused by a chimeric gene duplication formed from unequal crossover between the promoter sequence of *CYP11B1* gene, that encodes the 11 $\beta$ -hydroxylase, and the coding sequence of *CYP11B2* gene, that encodes aldosterone synthase. This genetic abnormality results in an ectopic expression of aldosterone synthase in the zona fasciculata, with regulation of the mineralocorticoid production exerted by ACTH instead of by the normal secretagogue, Ang II. Familial hyperaldosteronism type II is an autosomal dominant disorder and may be monogenic. This type of hyperaldosteronism is not ACTH-dependent and therefore is not suppressible by dexamethasone. GRA mutation testing is negative. Linkage analyses studies have shown an association with chromosome 7p22. Familial hyperaldosteronism type III is characterized by severe hypertension in early childhood associated with marked aldosteronism, hypokalemia, significant target organ damage and poor response to full doses of several classes of antihypertensive drugs, including spironolactone and amiloride. This finding distinguishes familial hyperaldosteronism type III from the other familial forms and sporadic primary aldosteronism, because spironolactone is usually successful in controlling blood pressure in these familial forms, while type III patients do not respond and require bilateral adrenalectomy. Important advances made in the past year have included identification of *KCNJ5* potassium channel mutations in the pathogenesis of both aldosterone-producing adenomas and familial hyperaldosteronism type III [14–16].

**Table 12.1** Current and emerging treatment strategies for primary aldosteronism

Subtype	First-line treatment	Second-line treatment
Unilateral	Unilateral laparoscopic adrenalectomy	Spironolactone Eplerenone Aldosterone synthase inhibitors
Bilateral	Spironolactone Eplerenone Aldosterone synthase inhibitors	
Glucocorticoid-remediable aldosteronism	Low-dose glucocorticoids (hydrocortisone or prednisone)	Spironolactone Eplerenone (preferable in children) Aldosterone synthase inhibitors

## Current and Emerging Treatment

The therapeutic goals involve not only normalization of blood pressure and plasma potassium levels, but also reduction of the increased cardiovascular morbidity and mortality associated with excessive aldosterone secretion. The identification of the cause helps to implement the most appropriate treatment. Table 12.1 summarizes the first-line and second-line therapeutic options for the subtypes of primary aldosteronism, which are discussed in more details below.

## Surgical Treatment

The recommended treatment in patients with unilateral adrenal adenoma or unilateral hyperplasia is unilateral laparoscopic adrenalectomy [11]. If the patient refuses surgery or there are contraindications for the procedure, aldosterone antagonists should be initiated. Total reversion of hypertension, with no need for any antihypertensive drug, occurs in 50 % of patients treated with surgery, whereas normalization of plasma potassium levels is observed in virtually all patients. Normalization of blood pressure is usually achieved 1–6 months after the surgical procedure. Chances of cure increase in patients with no other hypertensive family members and using one or two classes of antihypertensive medications. The laparoscopic technique is considered the best choice due to reduced pain, shorter hospitalization, and lower costs. Preoperative surgical care should be directed to maintain adequate blood pressure and potassium levels.

## Medical Treatment

Bilateral hyperplasia and GRA should be treated medically. This therapy is also employed for all patients who decline or are not considered for surgery. Mineralocorticoid receptor antagonists that reduce blood pressure and promote cardiovascular protection from the deleterious effects of aldosterone are the drugs of choice to treat primary aldosteronism [4–7, 10–12, 17].

Spironolactone has been used for more than 4 decades. Treatment can be started with doses of 12.5–25 mg in a single daily administration, which can be progressively increased up to 400 mg/day to achieve a high-normal serum potassium concentration, without adding oral potassium supplementation. Maintenance doses usually range between 25 and 100 mg/day. Plasma potassium should be monitored, and special care should be taken in elderly patients with diabetes or renal dysfunction. Concomitant use of salicylates can decrease the effectiveness of spironolactone. The main adverse effects are dose dependent and include erectile dysfunction, pain, and increased sensitivity of the breasts in men and women, and changes in the menstrual cycle of premenopausal women. Small dosages of thiazide diuretics help prevent an excessive increase in potassium and better control blood pressure.

Eplerenone is a selective antagonist of the mineralocorticoid receptors with minimal effect on the sex steroid receptors. In comparison with spironolactone, it is better tolerated, more expensive and must be started in a dose of 25 mg twice daily, titrated upward to 100 mg/day. It is an

alternative for patients presenting with adverse events during spironolactone therapy, as clinical trials comparing both drugs have shown similar antihypertensive effects [4, 18]. Side effects include dizziness, headache, fatigue, diarrhea, hypertriglyceridemia, and elevated liver enzymes.

Other drugs that can be used include antagonists of the sodium channels in renal epithelium, such as amiloride and triamterene. They do not have an antihypertensive efficacy similar to spironolactone, but are potassium sparing diuretics and have no sexual side effects. Finally, calcium channel antagonists and blockers of ACE 1 and 2 might be employed in some situations [4, 11].

Aldosterone synthase inhibitors are emerging as promising treatment agents acting as aldosterone antagonists—inhibiting its formation and preventing the reactive increases in aldosterone levels and their mineralocorticoid receptors-independent effects [19]. Several aldosterone synthase (CYP11B2) inhibitors are being developed. Fadrozole, an aromatase inhibitor or its dextroenantiomer (FAD286), has been shown to inhibit aldosterone synthase and to reduce mortality, cardiac hypertrophy, albuminuria, cell infiltration, and matrix deposition in the kidney in double transgenic renin rats (dTGR), yet without a profound effect on blood pressure [20]. Another agent, LCI699, was shown to reduce 24-h ambulatory systolic blood pressure and effectively suppress supine plasma aldosterone concentrations in patients with primary aldosteronism [21, 22]. Although plasma cortisol concentrations did not change, the ACTH concentrations were elevated, the plasma cortisol response to ACTH stimulation was blunted, and the plasma potassium concentration was increased.

The main clinical goal for aldosterone-synthase inhibitors is to be as good as the mineralocorticoid receptor antagonists for blood pressure reduction, with better tolerability. LCI699 was only modestly effective in patients with primary aldosteronism, with the demonstration that 1 mg of LCI699 was not superior to 50 mg of eplerenone in blood pressure reduction in patients with stage 1 and 2 hypertension. As a consequence, the development of LCI699 was stopped in 2010 in favor of seeking more specific inhibitors. Future studies are needed to address

the dose–response relationship, clinical implications and the potential blood pressure-independent organ-specific effects of these new agents [21, 22].

For patients with confirmed diagnosis of GRA, chronic use of physiologic doses of glucocorticoid is the first-line therapy. Care should be taken to not produce Cushing's syndrome by excessive doses of glucocorticoids, especially when dexamethasone is employed in children. Preferable drugs are hydrocortisone (10–12 mg/m<sup>2</sup> per day) or prednisone in equivalent doses, which ideally should be taken at bedtime to suppress the early morning ACTH surge. Treatment with mineralocorticoid receptor antagonists can be as effective as glucocorticoids, with the potential advantages of avoiding the iatrogenic side effects [11].

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## Hyperdeoxycorticosteronism

This is a distinct form of mineralocorticoid excess characterized by hypertension, hypokalemia, low aldosterone, low renin and excessive production of 11-deoxycorticosterone (DOC). Medical disorders associated with hyperdeoxycorticosteronism include two forms of congenital adrenal hyperplasia (11 $\beta$ -hydroxylase and 17 $\alpha$ -hydroxylase deficiency), DOC-producing tumors, primary cortisol resistance, and genetic or acquired forms of apparent mineralocorticoid excess (AME) [23].

11 $\beta$ -hydroxylase deficiency accounts for about 5 % of all cases of congenital adrenal hyperplasia, with more than 40 mutations described in *CYP11B1* gene. Diagnosis is made by the demonstration of high plasma levels of DOC and 11-deoxycortisol. There is also an excessive secretion of adrenal androgens that causes acne, hirsutism and virilization in girls. Boys may present with pseudoprecocious puberty. 17 $\alpha$ -hydroxylase deficiency is a rare cause of congenital adrenal hyperplasia whose diagnosis is usually suspected at time of puberty, due to primary amenorrhea in genetic females, or pseudohermaphroditism or female phenotype in genetic 46,XY males. The main laboratorial findings to confirm the diagnosis are low levels of plasma adrenal

androgens, 17 $\alpha$ -hydroxyprogesterone, aldosterone, ARR, and cortisol, associated with high levels of DOC, corticosterone, and 18-hydroxycorticosterone. Glucocorticoid replacement is the treatment of choice for both disorders [23].

DOC-producing tumors are usually large and malignant, and they can also secrete androgens and estrogens causing virilization in women and feminization in men. Surgical resection of the tumor is the recommended therapy. Primary cortisol resistance is a rare familial syndrome caused by defects in the glucocorticoid receptors and the steroid-receptor complex, characterized by alkalosis, elevated serum levels of cortisol, adrenal androgens, and DOC. The signs and symptoms of Cushing's syndrome are typically absent. AME is associated with reduced activity of HSD11B2 enzyme, which normally inactivates cortisol in the kidney. It can be hereditary or secondary to the use of licorice or some chewing tobaccos. Patients with AME present metabolic alkalosis, normal cortisol levels, and an altered ratio of cortisol to cortisone in a 24-h urine collection, up to tenfold above the normal values. Mineralocorticoid receptor antagonists or dexamethasone are used in the treatment of AME and primary cortisol resistance [23].

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## **Pheochromocytoma and Paragangliomas**

Pheochromocytoma is a catecholamine-producing tumor derived from chromaffin cells. When such tumors arise outside of the adrenal gland, they are termed extra-adrenal pheochromocytomas or paragangliomas. The term paraganglioma is sometimes also used for tumors originated from parasympathetic tissue in the head and neck, most of which do not produce catecholamines. The word pheochromocytoma (in Greek, *phios* means dusky, *chroma* means color, and *cytoma* means tumor) refers to the color the tumor cells acquire when stained with chromium salts [24].

The clinical presentation of a pheochromocytoma varies from an adrenal incidentaloma to a picture of severe hypertension and life-threatening arrhythmias due to intense, albeit frequently

episodic, catecholamine secretion. Fortunately, these tumors are potentially curable. Therefore, early detection is crucial, making a systematic and effective diagnostic approach clearly warranted [25].

## **Location of the Tumors, Biosynthesis and Metabolism of Catecholamines**

Pheochromocytomas are usually derived from the adrenal medulla, but may develop from chromaffin cells in or near sympathetic ganglia. Over 90 % of pheochromocytomas are located within the adrenal glands, and 98 % are within the abdomen. Extra-adrenal locations include the organ of Zuckerkandl (close to origin of the inferior mesenteric artery), bladder wall, heart, mediastinum, and carotid and glomus jugulare bodies [24]. The adrenal medulla, part of the sympathetic nervous system, consists of certain cells known as chromaffin cells, characterized by excessive production of catecholamines.

The clinical manifestations of a pheochromocytoma result from excessive catecholamine secretion by the tumor. The rate-limiting step in catecholamine biosynthesis involves conversion of tyrosine to 3,4-dihydroxyphenylalanine (L-dopa) by the enzyme tyrosine hydroxylase [26]. This enzyme is largely confined to dopaminergic and noradrenergic neurons of the central nervous system, and to sympathetic nerves and adrenal and extra-adrenal chromaffin cells in the periphery. Other sites of catecholamine synthesis include certain non-neuronal cells of the gastrointestinal tract and kidneys [27]. After that, L-dopa is converted to dopamine in the cytosol of the cell and transported into the cell's chromaffin granules, where it is either stored or converted to norepinephrine by the enzyme dopamine  $\beta$ -hydroxylase. Some of the norepinephrine migrates back into the cytosol, where it is converted into epinephrine by the enzyme phenylethanolamine *N*-methyltransferase (PNMT). Then, the epinephrine returns to the chromaffin granules where it is stored. In the adult adrenal medulla, epinephrine (80–85 %) is the predominant catecholamine stored and secreted [28].

The catecholamines are inactivated by two enzymes, catechol-O-methyl-transferase (COMT) and monoamine oxidase (MAO), in the liver. Norepinephrine and epinephrine are metabolized by COMT to normetanephrine and metanephrine, respectively. In a next step, normetanephrine and metanephrine are metabolized to vanillylmandelic acid by MAO plus aldehyde dehydrogenase [28]. Unaltered epinephrine and norepinephrine and their inactive metabolites are finally excreted into the urine.

Most pheochromocytomas produce predominantly norepinephrine, many produce both norepinephrine and epinephrine, and a minority produce predominantly epinephrine [4]. Dopamine, which is usually efficiently converted to norepinephrine, is a minor component. However, some cases of paragangliomas have been identified that produce mainly dopamine [27, 29]. Pheochromocytomas also store and secrete in the blood many peptides like endothelin, erythropoetin, parathyroid hormone-related peptide, neuropeptide-Y, and chromogranin-A. Differently from the adrenal medulla, pheochromocytomas are not innervated, and catecholamine discharge is not precipitated by neural stimulation. The trigger for catecholamine release is unclear, but multiple mechanisms have been postulated, including direct pressure, medications, and changes in tumor blood flow [24].

## Pathology and Molecular Genetics

The essential histopathologic characteristics are very similar among pheochromocytomas. Sporadic pheochromocytomas are generally solitary, well-circumscribed, well-vascularized, encapsulated tumors, with characteristic histopathological features [30]. Approximately 10 % of pheochromocytomas are malignant. Histologic criteria of cellular atypia, numerous mitoses, and invasion of adjacent tissues or vessels do not identify, with certainty, which tumors have the potential to metastasize. Actually, the 2004 World Health Organization criteria define malignancy in pheochromocytoma by the presence of metastases and not by local invasion [27, 30].

Common metastatic sites include bone, liver, and lymph nodes.

Improvements in genetics, diagnosis, and treatment of pheochromocytomas have altered the approaches to these tumors in recent years. The formerly used rule of “10 % tumor” for pheochromocytoma (10 % are bilateral, 10 % are found in children, 10 % are inherited, 10 % are malignant, and 10 % are found outside the adrenal gland) has been challenged [4, 31]. According to the latest studies, up to 24 % of tumors among patients with nonsyndromic pheochromocytoma may be hereditary. As shown in Table 12.2, there are associations with multiple endocrine neoplasia type 2 (MEN-2A or MEN-2B), neurofibromatosis type 1 (NF-1), von Hippel-Lindau (VHL) syndrome, and with germ-line mutations of genes encoding succinate dehydrogenase subunits B, C, and D (SDHB, SDHC, SDHD) [4, 32]. This novel genetic knowledge has led to routine screening in patients with identified mutations, even in the absence of typical clinical signs and symptoms of pheochromocytoma. Because hereditary tumors generally occur at a younger age than sporadic tumors, age at presentation is an important factor to consider when deciding to test for disease-causing genes. Besides patient's age, the biochemical profile of catecholamine secretion, localization of the primary tumor, and previous family history must be carefully evaluated to choose a proper genetic test. For instance, MEN-2- and NF-1-related pheochromocytoma always secrete epinephrine, while those related to VHL secrete norepinephrine, and some related to SDHB cause elevation of dopamine together with norepinephrine. MEN-2, VHL, and NF-1 tumors are almost always found in the adrenal gland, whereas SDHB-related tumors are found in extraadrenal localizations. In those patients with malignant disease secondary to an extra-adrenal paraganglioma, around half of them harbor SDHB mutations [4].

## Prevalence and Clinical Presentation

The annual incidence of pheochromocytoma is around 400 cases per 1 million hypertensive patients. In the general population, the annual



**Table 12.2** Hereditary disorders associated with pheochromocytomas/paragangliomas

Syndrome	Gene	Clinical features
MEN 2	RET	
Type A		Medullary thyroid carcinoma Primary hyperparathyroidism
Type B		Medullary thyroid carcinoma Ganglioneuromas Marfanoid habitus
VHL disease	VHL	
Type 2A		Hemangioblastoma Low risk of renal cell carcinoma
Type 2B		Hemangioblastoma High risk of renal cell carcinoma
Type 2C		Pheochromocytoma only
NF-1	NF-1	Neurofibromas <i>Café-au-lait</i> spots Axillary or inguinal freckling Optic nerve glioma
Paraganglioma syndromes (SDH)	SDH	
SDHD		Head and neck paraganglioma Pheochromocytoma Extra-adrenal paraganglioma
SDHB		Head and neck paraganglioma Renal carcinoma Pheochromocytoma Extra-adrenal paraganglioma

incidence of the tumor is estimated to be 1.5–2.1 cases per 1 million individuals [28]. The prevalence of pheochromocytoma and paraganglioma is estimated to lie between 1:6,500 and 1:2,500 in the United States [32]. About 0.1–0.6 % of hypertensive patients harbor a pheochromocytoma and autopsy series reveal prevalence of 0.05 % [4, 33]. In a retrospective study from the Mayo Clinic, 50 % of cases were diagnosed at autopsy [34].

Pheochromocytoma is often considered in many clinical scenarios in virtue of its numerous presentations. The diverse manifestations of this tumor reflect variations in the hormones it releases, their patterns of release, and the individual-to-individual differences in catecholamine sensitivities [35, 36]. The mean age of diagnosis is about 40 years, although the tumors can occur in any age, from early childhood until late in life. There is a slightly higher female preponderance. It is worthy to mention that the severity of clinical symptoms does not always correlate with plasma catecholamine levels [35,

36]. A pheochromocytoma can be asymptomatic for years, and some grow to a very considerable size before any clinical manifestation. Nowadays, approximately 25 % of all pheochromocytomas are discovered incidentally during imaging studies for unrelated disorders, comprising about 5 % of all adrenal incidentalomas [33].

Hypertension (sustained or paroxysmal, equally present) is the most common and prominent clinical sign, present in 85–90 % of the cases. Norepinephrine-secreting tumors are usually associated with sustained hypertension, tumors that secrete large amounts of norepinephrine with epinephrine are associated with episodic hypertension, and pure epinephrine-secreting tumors can cause hypotension rather than hypertension [4]. Clinical findings, such as headache, profuse sweating, palpitations, and pallor, are highly indicative of pheochromocytoma. If signs and symptoms are of paroxysmal nature, the suspicion of a pheochromocytoma is strengthened [36]. Acute heart failure, cardiogenic pulmonary edema, intracranial hemorrhage can be initiated

by catecholamine crisis. Anesthesia, tumor manipulation, and chemical compounds or drugs (e.g., glucagon, radiographic contrast substances, tyramine, metoclopramide, and tricyclic antidepressants) are the most well-known stimuli to elicit a catecholaminergic surge [33].

Orthostatic hypotension can occur from decreased sympathetic reflexes. On a background of hypertension, this finding provides an important evidence for the presence of a pheochromocytoma. Normal blood pressure is relatively common in patients with dopamine-producing paragangliomas [4, 29]. Weight loss may result from chronic accelerated metabolism. Hyperglycemia can be a consequence of the effects of catecholamines on beta cells of the pancreas. Sometimes, feelings of panic or anxiety dominate the clinical presentation [33].

During pregnancy or delivery, pheochromocytoma may present as a hypertensive crisis and must be distinguished from eclampsia. Pheochromocytoma occurring during pregnancy carries a grave prognosis, with maternal and fetal mortality rates of 48 and 55 %, respectively. However, maternal mortality is virtually eliminated and the fetal mortality rate is reduced to 15 % if the diagnosis is made antenatally [24].

## Biochemical Diagnosis

Biochemical assays are now much more sophisticated than in past years, and for this reason, it is somewhat easier to confirm the biochemical diagnosis of inappropriate catecholamines levels. Traditionally, measurement of urinary catecholamines has been the most widely used test, but evaluation of urinary catecholamines metabolites or plasma catecholamines has also been recommended [37]. Screening tests with high sensitivity are necessary, so that negative results provide confidence that the diagnosis has not been missed (Table 12.3). It is now clear that catecholamines are metabolized within chromaffin cells to metanephrines (i.e., norepinephrine to normetanephrine and epinephrine to metanephrine). Consistent with these concepts, studies have confirmed that

**Table 12.3** Sensitivity and specificity of biochemical tests for diagnosis of pheochromocytoma/paraganglioma

Test	Sensitivity (%)	Specificity (%)
Plasma-free metanephrines	99	89
Plasma catecholamines	84	81
Urinary catecholamines	86	88
Urinary-fractionated metanephrines	97	69
Urinary total metanephrines	77	93
Urinary vanillylmandelic acid (VMA)	64	95

measurements of fractionated metanephrines (i.e., normetanephrine and metanephrine measured separately) in urine or plasma provide superior diagnostic sensitivity to measurements of the parent catecholamines [37–39]. Plasma fractionated metanephrines have a sensitivity and specificity of 98 and 92 %, as compared to 85 and 86 %, respectively, for urinary catecholamines. Moreover, values of plasma metanephrine more than fourfold above the upper reference limit is associated with almost 100 % probability for the presence of the tumor [4].

Current recommendations are that initial testing for pheochromocytoma must estimate fractionated metanephrines in plasma, urine, or both [32, 40]. Blood sampling should be performed at a supine position after 15–20 min of intravenous catheter insertion. Food, caffeinated beverages, strenuous physical activity, or smoking are not allowed at least 8–12 h before the testing [32]. Also, several common drugs that affect catecholamine and metabolite levels should be avoided, like tricyclic antidepressants, beta-blockers, benzodiazepines, L-dopa, methyl dopa, and reserpine [41].

In equivocal cases, some pharmacological tests can be performed. The clonidine suppression test uses the properties of this drug to decrease central sympathetic outflow in normal subjects. Failure to suppress plasma norepinephrine by more than 50 %, and into the normal range, within 2–3 h after administration of an appropriate dose (0.2–0.3 mg) of clonidine, is highly suggestive of a pheochromocytoma [42].

## Imaging Procedures

Once the diagnosis of pheochromocytoma is confirmed by a positive biochemistry, the next step is to locate the tumor. Imaging studies should not be used as a screening test, due to the risk of discovering an incidentaloma. CT scan can be used to localize adrenal tumors >1 cm and extra adrenal tumors >2 cm, with approximately 95 % of sensitivity and 65 % of specificity. MRI with or without gadolinium enhancement is superior for the detection of extra-adrenal tumors [41]. The T2-weighted MRI has a better specificity due to “lightning up” phenomena of the chromaffin cells.

Tumors in unusual sites and metastases can be identified with metaiodobenzylguanidine (MIBG) scintigraphy, which is effective to locate pheochromocytomas of all types with high specificity, as MIBG is concentrated by the tumor’s uptake of precursor amines [43]. Also, MIBG has the advantage of performing noninvasive scintigraphy of the entire body in a single procedure.

An advanced imaging technique occasionally employed in difficult pheochromocytoma cases is the positron emission tomography (PET) scanning. PET with <sup>18</sup>F-fluorodeoxyglucose scanning can be useful if other imaging procedures are negative, often in more rapidly growing dedifferentiated tumors that have lost the ability to accumulate more specific drugs [33]. Somatostatin receptor imaging, other types of PET that utilize different compounds, or even selective venous sampling of the vena cava at various levels can sometimes help to locate the tumor [4, 42].

## Principles of Management

Surgery is the primary treatment of pheochromocytoma and paraganglioma. The surgical approach varies depending on tumor size, location, and surgeon’s personal attitude and experience. However, laparoscopic surgery is now the technique of choice for resection of adrenal and extra-adrenal tumors. Observational studies have shown that laparoscopic procedure decreases postoperative morbidity, hospital stay, and expense, as com-

pared with the conventional transabdominal technique for tumor removal [32].

## Perioperative Management

The goal of medical management at this point is to control blood pressure and block the cardiovascular consequences of increased amounts of circulating catecholamines. It is recommended that all patients with pheochromocytoma undergo  $\alpha$ -adrenergic blockade, which should be started 1–2 weeks prior to surgery to help reduce blood pressure lability, intraoperative blood loss, and arrhythmias. There are several  $\alpha$ -blockers that are commonly used in patients with pheochromocytoma. Phenoxybenzamine has been used since the 1950s and is a long-acting, non-competitive alpha-antagonist [44]. The more selective, competitive, postsynaptic  $\alpha$ 1-blockers (prazosin, terazosin, doxazosin) have a shorter duration of action and provide incomplete  $\alpha$ -blockade, so failures have been described [42]. A  $\beta$ -adrenoreceptor blocker (e.g., propranolol or atenolol) could be included after several days of  $\alpha$ -adrenergic blockade. This addition is especially useful in patients who also have tachyarrhythmias. The  $\beta$ -blocker must be given only after achieving effective  $\alpha$ -blockade to avoid unopposed  $\alpha$ -adrenergic agonism.

During surgery, tumor manipulation may stimulate sudden catecholamine release, resulting in a marked increase in blood pressure and bleeding from small vessels. Immediate cessation of tumor manipulation will help the anesthesiologist to normalize the blood pressure [44]. Sodium nitroprusside, phentolamine, prazosin, nitroglycerin, and various other agents, such as magnesium sulfate, nicardipine, and diltiazem, have been used to control intraoperative rises in blood pressure.  $\beta$ -blockers have been used to control tachycardia and blood pressure. After the adrenal veins are ligated and the tumor removed, hypotension may occur. This is frequently amenable to modest fluid load and discontinuation of vasodilators and  $\beta$ -blockers [45]. For the management during pregnancy, infusion

of a  $\alpha$ -blocker or nitroprusside with delivery by cesarean section is the first-choice option [46].

## Postoperative Follow-up

Frequent blood pressure monitoring is very important postoperatively. Patients are prone to develop hypotension due to acute withdrawal of catecholamines after resection of the tumor. Return to normal may require as long as two weeks due to the large amounts of sympathomimetic compounds stored in the body. Failure to normalize might indicate the presence of residual, second, or metastatic tumor. Up to one-third of patients may be left with some sustained hypertension despite normal catecholamines, probably due to damage of renal vasculature. All patients should have long-term follow-up because metastases may manifest after long periods [46].

## Treatment of Malignant Pheochromocytoma

These tumors are poorly responsive to radiotherapy or chemotherapy [41]. Surgical debulking is sometimes necessary to decrease catecholamine level. High-dose of radioactive MIBG has been tried with some success to ablate primary and metastatic sites. Alpha-methyl-tyrosine has been used in inoperable cases [42]. Many other experimental and targeted therapies have been tried, including sunitinib (a receptor tyrosine kinase inhibitor), imatinib mesylate (a tyrosine kinase inhibitor), thalidomide, everolimus, temozolomide, and trastuzumab [41].

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## Cushing's Syndrome

### Prevalence and Etiology

Cushing's syndrome is the clinical condition characterized by a prolonged and inappropriate state of hypercortisolism. The commonest cause of Cushing's syndrome is the iatrogenic exposure to exogenous glucocorticoids. Endogenous Cushing's

syndrome can be ACTH-dependent—caused by excessive secretion of ACTH by a pituitary adenoma (Cushing's disease) in 75 % of cases, or by an ectopic ACTH-secreting (rarely CRH-secreting) tumor in 15 % of cases—or ACTH-independent. The latter accounts for about 20 % of cases and is caused by a benign (adenoma) or malignant (carcinoma) adrenal tumor in most instances, or more rarely, by macronodular adrenal hyperplasia, primary pigmented nodular adrenal disease or McCune–Albright syndrome [4, 47].

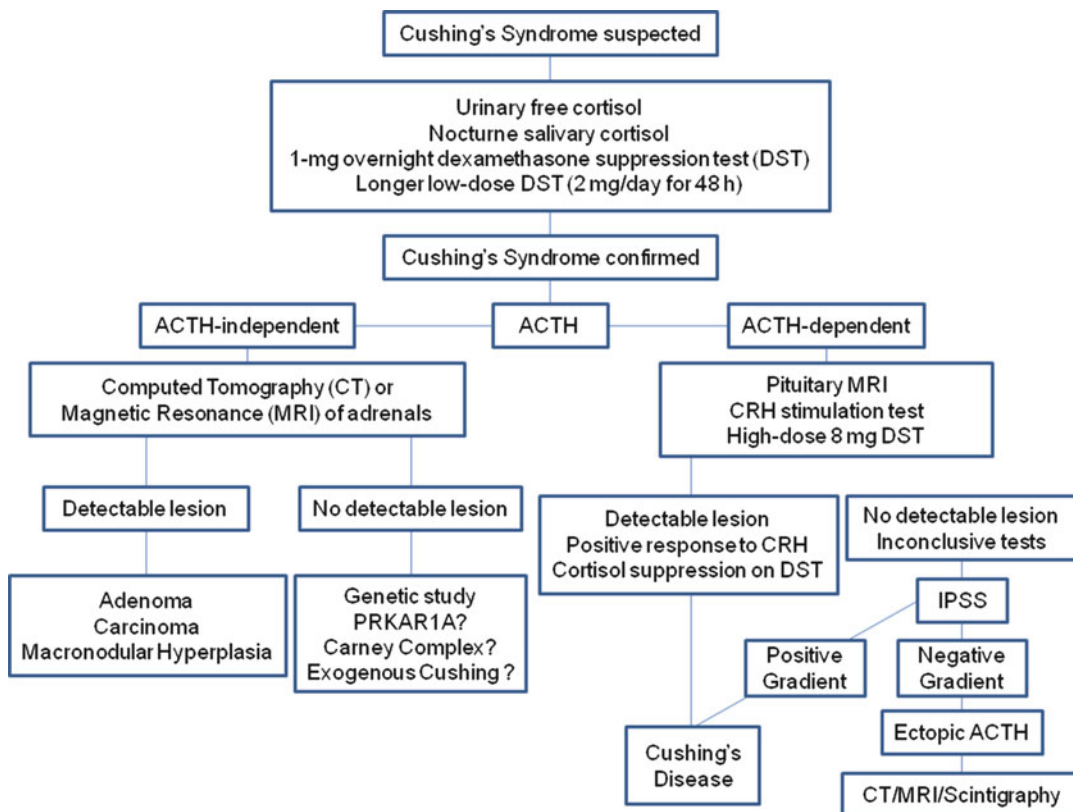
Endogenous Cushing's syndrome is not a common disease, with a reported incidence of 2–5 cases per million people. However, these numbers increase substantially to 2–5 % in certain subpopulations, such as patients with uncontrolled type 2 diabetes, obesity, osteoporosis and hypertension [47, 48].

On the other hand, hypertension is present in approximately 80 % of adult patients with endogenous Cushing's syndrome, being more frequent (95 %) in ectopic Cushing's syndrome, and less frequent (47 %) in children and adolescents. Only about 20 % of patients with iatrogenic Cushing's syndrome have hypertension, which correlates with the daily dose of glucocorticoid [4, 47].

### Physiopathology of Hypertension

Cushing's syndrome is associated with high risk of vascular disease and increased mortality. In addition to hypertension, other findings usually present in hypercortisolemic patients contribute to this association, such as impaired glucose tolerance, diabetes, dyslipidemia, and visceral obesity.

The physiologic sleep-related decrease in blood pressure might be lost or reduced in patients with Cushing's syndrome in comparison with normal individuals or patients with essential hypertension. Moreover, there are numerous mechanisms underlying the development of hypertension in patients with Cushing's syndrome, including mineralocorticoid effects caused by the supraphysiological cortisol levels, enhanced activation of the RAAS, impaired



**Fig. 12.2** Diagnostic approach for endogenous Cushing's syndrome

vasodilatation, increased vascular response to catecholamines, and other cortisol effects on peripheral and systemic vasculature [47].

### Screening and Diagnostic Approach

When hypertension occurs in young individuals, Cushing's syndrome should be suspected, especially in the presence of signs or symptoms such as plethora, purplish striae greater than 1 cm, proximal muscle weakness, easy bruising, hyperglycemia, unusual infections, or unexplained osteoporosis. In children, weight gain and growth retardation are more prominent. Moreover, sub-clinical hypercortisolism should be considered in patients with resistant hypertension and adrenal incidentaloma [4, 49, 50].

Cushing's syndrome is challenging to diagnose (Fig. 12.2). Initial testing to confirm the presence of hypercortisolism involves elevated levels of urinary free cortisol (UFC), elevated late night salivary cortisol, no suppression of serum cortisol levels on 1-mg overnight dexamethasone suppression test (DST) or on longer low-dose DST (2 mg/day for 48 h) [50]. Once biochemical diagnosis is established with at least two abnormal tests, the next step is to measure plasma ACTH levels to distinguish between ACTH-independent (low normal or undetectable ACTH values) and ACTH-dependent (elevated or inappropriately normal ACTH values) causes of Cushing's syndrome. Then, imaging studies are employed to reveal the underlying etiology: if ACTH-independent, CT or MRI of adrenals, which frequently revealed the responsible lesion;

if ACTH-dependent, pituitary MRI. In this case, a pituitary adenoma is visible in about 50–60 % of patients. For those ACTH-dependent cases with negative or equivocal pituitary imaging, the final diagnosis depends on the results of additional hormone measurements (CRH stimulation test and high-dose 8 mg DST) and/or bilateral inferior petrosal sinus sampling (IPSS). In the IPSS, a central-to-peripheral ACTH gradient greater than 2 at baseline (or 3 after CRH or DDAVP administration) indicates Cushing's disease. In the absence of a gradient, a search for an ectopic source should be performed using other imaging modalities, including CT, MRI, and scintigraphy [47, 50].

## Management of Hypertension

The main goal is to treat the cause of excess glucocorticoids, in most cases through surgical removal of a pituitary, adrenal or ectopic tumor. This approach can lead to resolution or improvement of hypertension, but in about one-third of adult patients a complete normalization of blood pressure is not achieved. By contrast, children and adolescents show complete resolution after surgical cure. Persistent hypertension after surgery correlates with the duration, but not the severity, of preoperative hypertension [4, 47].

Drugs that reduce glucocorticoid levels might be employed as adjunctive treatment. They include compounds that modulate ACTH release (dopamine agonists and somatostatin analogues in patients with Cushing's disease), promote adrenolytic effects by inhibiting steroidogenesis (ketoconazole and mitotane), or block glucocorticoid action (mifepristone). Metyrapone, another drug used to inhibit steroidogenesis, may exacerbate hypertension by increasing mineralocorticoid production [4, 47].

Cabergoline is the only dopamine agonist with some long-term efficacy in controlling patients with Cushing's disease. Normalization of cortisol levels with doses of 1–7 mg per week of cabergoline was reported on 40 % of patients after 24 months of follow-up [51]. The somatostatin analogues octreotide and lanreotide, which bind

mainly to the somatostatin receptor sst2, are not useful in Cushing's disease, as the high circulating levels of cortisol promote sst2 down-regulation [52]. By contrast, pasireotide—a cyclohexapeptide somatostatin analogue that binds to sst1, sst2, sst3 and sst5—can be effective and it was recently approved for treatment of Cushing's disease by the European Commission [53]. The control of hypertension depends on the successful control of hypercortisolemia, which is not uniformly obtained in all patients. Hence, the role of these drugs in the medical management of ACTH-dependent Cushing's syndrome is still under investigation [4, 47]. More recently, preliminary results of combined short-term therapy using ACTH release modulators with adrenolytic drugs have demonstrated normalization of cortisol levels or cortisoluria in a substantial number of patients, opening novel therapeutic perspectives [54].

Ketoconazole is the main steroidogenesis inhibitor used in Cushing's syndrome, inducing remission in up to 70 % of the cases. The starting dose is 200 mg twice daily and can be given up to 1,200 mg daily in four divided doses [4]. It has a rapid onset of action, but its long-term efficacy is limited due to its side effects and escape phenomenon, where ACTH secretion overrides control of hypercortisolemia. This escape phenomenon is less likely with very high doses of mitotane, presumably because of its adrenolytic effects. Mitotane is often started at doses of 250–500 mg at night, which can be titrated up to 4–12 g daily. However, the use of high doses and overtreatment with mitotane (as well as ketoconazole) is associated with increased toxicity and can result in adrenal insufficiency [4, 47].

Mifepristone is a type 2 glucocorticoid receptor (GR) antagonist, which also inhibits progesterone receptors. Recently, it has been approved in the United States for the treatment of hyperglycemia in adults with endogenous Cushing's syndrome who are not surgical candidates or have failed surgery [55]. A 6-month phase III study carried out in 50 subjects with Cushing's syndrome who were either glucose intolerant or hypertensive, found a significant improvement in glucose tolerance and blood pressure in 60 and

43 % of patients, respectively [56]. Adrenal insufficiency may occur as a result of excess glucocorticoid receptor blockade, which must be recognized based only in clinical criteria. Other side effects include hypokalemia and hypertension, both occurring as a result of unopposed activation of mineralocorticoid receptors in the kidney tubules by cortisol excess. In women, endometrial hyperplasia and irregular menstrual bleeding may occur as a result of progesterone receptors inhibition [55].

Patients with Cushing's usually need antihypertensive therapy with more than one drug to control their blood pressure. ACE inhibitors and Ang II receptor blockers are the first choices, with good response observed in almost 50 % of patients. If necessary, thiazide diuretics, adrenergic and calcium channel blockers may be added to the therapy [23, 47]. However, it is important to emphasize that might be very cumbersome to control blood pressure without normalization of hypercortisolemia.

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## Others Endocrine Disorders

Other endocrine disorders associated with hypertension include acromegaly, hypothyroidism and hyperthyroidism, and primary hyperparathyroidism. In general, the diagnosis of these conditions is straightforward and hypertension is just one piece of the puzzle. This means that these conditions should be investigated only in hypertensive subjects with other suspicious clinical or laboratorial findings. As a general rule, treatment of the underlying disorder is the main step to control blood pressure, but when remission is not observed, specific antihypertensive drugs should be initiated.

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### Epidemiology of Hirsutism and Virilization

Hirsutism is one of the commonest medical complaints among women of reproductive age [1]. The actual prevalence of hirsutism in adults ranges from 3 to 15 % in Blacks and Whites [2–5], but is somewhat lower in Asians (1–3 %) [6].

Recent epidemiological surveys have added data concerning hirsutism restricted to adolescence and youth and demonstrated that this condition is still very frequent from the post-menarchal years, with a prevalence ranging from 8 to 13 % [7–9].

At variance, virilization is a rare condition, but it may present from prenatal to adult life, involving also the neonatal, prepubertal, and adolescent periods with a prevalence varying with the cause and the date of appearance of the disorder. In particular, the most frequent causes of virilization in the prenatal/neonatal periods of life are some monogenic enzymatic adrenal deficiencies,

CCAH, due to 21-hydroxylase, 11-hydroxylase, 3 $\beta$ -hydroxysteroid-dehydrogenase, P450-oxidoreductase, or aromatase defects [10, 11], that have an overall prevalence of about 1:20,000 female newborns per year. The prevalence of virilization decreases switching to prepubertal, pubertal, and adolescent periods, where the principal cause is represented by rare adrenocortical tumors, whose worldwide annual incidence ranges from 0.3 to 0.38 per million children below the age of 15 years [12–15]. In adults, the prevalence of virilization is even more rare, being mainly caused by rare forms of ovarian androgen secreting tumors, the sex cord-stromal tumors, that account for less than 0.5 % of all ovarian neoplasms [16].

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### Etiology of Hirsutism and Virilization

Functional causes account for most of cases of hirsutism. They include polycystic ovary syndrome (PCOS), idiopathic hyperandrogenism, and idiopathic hirsutism. PCOS, that is the most common cause of hirsutism, is characterized by the combination of hirsutism and/or biochemical hyperandrogenism with anovulatory cycles and/or polycystic ovarian morphology [17]. Idiopathic hyperandrogenism is characterized by the combination of hirsutism with biochemical hyperandrogenism but normal ovulatory cycles and normal ovarian morphology [18]; idiopathic

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**Table 13.1** Causes of female virilization according to age

Age	Adrenals	Ovaries	Others
Prenatal/neonatal	46,XX CCAH:	Maternal androgenizing tumors	Maternal drugs
Prepubertal	46,XX NCCAH Adrenal adenomas Adrenal carcinomas Adrenal hyperplasia 11 $\beta$ -HSD1 deficiency	Androgen producing tumors (sex cord stromal; gonadoblastoma)	
Pubertal/adolescence	Adrenal adenomas Adrenal carcinomas Adrenal hyperplasia Cushing's syndrome	Androgen producing tumors (sex cord stromal; gonadoblastoma)	Hyperprolactinemia
Adult	Adrenal adenomas Adrenal carcinomas Adrenal hyperplasia Cushing's syndrome	Androgen producing tumors (sex cord stromal) Hyperthecosis	Hyperprolactinemia Exogenous DHEA intake
Pregnancy	Maternal adenomas/ carcinomas	Luteoma	Placental aromatase deficiency Fetal PORD
Post-menopausal	Adrenal adenomas Adrenal carcinomas	Androgen producing tumors (sex cord stromal) Hyperthecosis	

CCAH classic congenital adrenal hyperplasia, NCCAH non-classic congenital adrenal hyperplasia, 11 $\beta$ -HSD1 11 $\beta$ -hydroxysteroid dehydrogenase type 1, PORD cytochrome P450 oxidoreductase deficiency

hirsutism is characterized by hirsutism in the presence of normal androgens, ovulatory cycles, and normal ovaries [19].

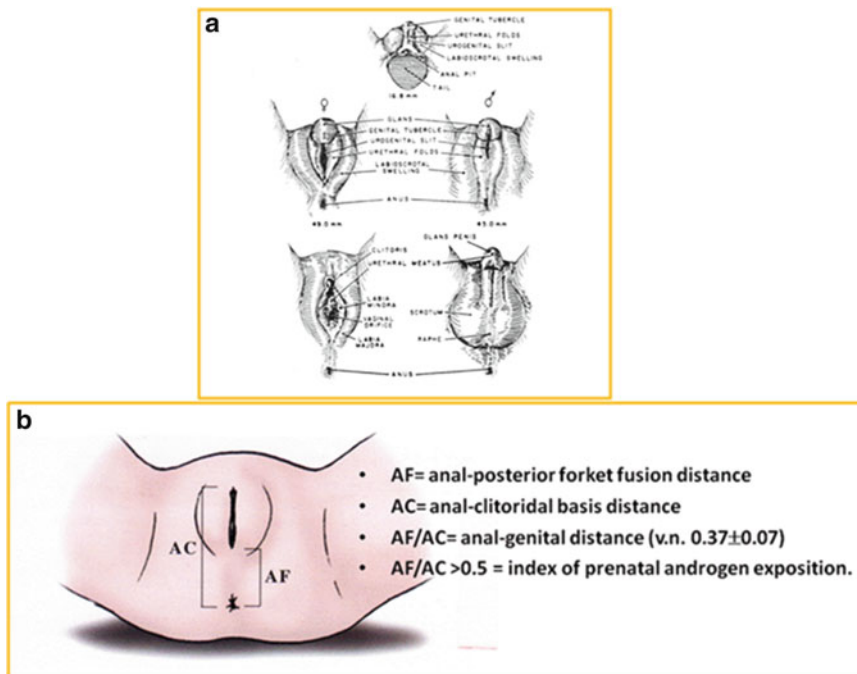
Less common but an important cause of hirsutism are different forms of non-classic congenital adrenal hyperplasia (NCCAH), mainly represented by 21-hydroxylase deficiency, while adrenal or ovarian androgen-secreting tumors, gestational hyperandrogenism, drug-induced hirsutism, ovarian hyperthecosis, Cushing's syndrome, acromegaly, hypothyroidism, and hyperprolactinemia are very uncommon, but should always be considered in the diagnostic approach to hirsutism [2].

The latter causes become much more consistent when virilism is present. The more frequent causes of virilization according to age of onset are shown in Table 13.1.

### Pathophysiology of Hirsutism and Virilization

There are three structural types of hair on the human body: lanugo is a soft hair that covers the skin of the fetus, but disappears soon after the

birth; vellus is a soft hair, usually non-pigmented and with a diameter less than 0.03 mm covering much of the body in men and women; terminal hair is longer, pigmented and coarser in texture and with different extents of expression in men and women. In particular, females have terminal hairs only in the eyebrows, eyelashes, scalp, pubis, and axillae [20]. Hair arises from a complex and highly dynamic structure—the hair follicle, which consists of several components and has a rhythmic growth cycle [21]. The hair follicle growth cycle is made up of three major phases: anagen (a stage of rapid growth), telogen (a stage of relative quiescence), and catagen (apoptosis-mediated regression) [22]. Hirsutism follows an alteration of the hair follicle cycle, in particular a prolongation of the anagen phase with a consequent transformation of vellus into terminal hairs. This alteration appears under the effect of androgens that are triggered and involved in the regulation of growth of sexual hair. Androgens active on hair follicle are testosterone (T) and dihydrotestosterone (DHT), which may be generated via a de novo synthetic pathway from cholesterol, and/or via a shortcut pathway from circulating dehydroepiandrosterone-sulfate



**Fig. 13.1** (a) External Genitalia development in females and males; (b) Anal–genital distance

(DHEA-S) [23]. Cutaneous testosterone may arrive from the circulation, principally synthesized in the adrenals and ovaries, and/or may be locally generated, since hair follicles are equipped with all the necessary enzymes for biosynthesis and metabolism of androgens [23]. DHT is almost entirely synthesized locally in a step catalyzed by the enzyme  $5\alpha$ -reductase [24]. Therefore, circulating androgen levels do not quantify the real exposure of hair follicle to androgens, since a quota is locally generated. Furthermore, cutaneous androgen effects also depend on the local expression and activity of the androgen receptor [22]. This justifies why the severity of hirsutism is always not correlated with circulating androgen concentrations.

Similarly, virilization results from the interaction between androgen concentration and local sensitivity to androgens. However, virilization also results from an excessive widespread exposure to androgens (mainly T and DHT), involving not only hair follicles but also sebaceous glands, muscle mass, adipose tissue, and external genitalia. Similarly to hirsutism, also for virilization the source of androgens is mainly

represented by the adrenals (from prenatal to pre-pubertal periods) and ovaries (after puberty until menopause), but a quota is peripherally or locally synthesized [25, 26]. The most deleterious effect of hyperandrogenism in females is certainly when it appears in the prenatal period, because it may cause ambiguous external genitalia [27].

At the start of life, in fact, the external genitalia are identical, regardless of the genetic or gonadal sex and consist of the genital tubercle, the urogenital folds, and the genital swellings (Fig. 13.1a). In a normal female fetus, when androgenic effects are lacking, the genital tubercle forms a clitoris, and the urethral folds and the genital swellings develop into the labia minora and majora, respectively (Fig. 13.1a, left side) [28]. On the contrary, when hyperandrogenism takes place in utero, such as in a 46,XX fetus affected by CCAH, male genital differentiation occurs due to the elevated amounts of adrenal testosterone, which is produced from the seventh to eighth week of gestation. In this case the genital tubercle grows into a penis, the urethral folds fuse to create a tubular penile urethra with the tendency of the meatus to locate at the tip of the

penis, and the genital swellings join to form a scrotum (Fig. 13.1a; right side). In cases of milder androgen exposure (before the fourteenth week of gestational age), the posterior labial fusion results in an increased anal–genital distance (Fig. 13.1b). Since internal genitalia are not sensitive to androgens, the uterus, fallopian tubes, and the upper part of the vagina develop normally.

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## Key Points to the Diagnosis of Hirsutism and Virilization

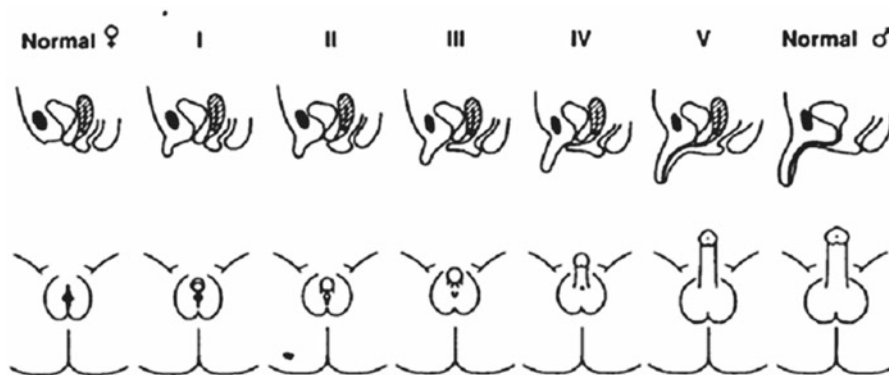
The diagnosis of hirsutism and virilization is based on the quantification of the problem and on the definition of the etiology. The quantification of hirsutism or virilization is obtained by a physical exam through the use of subjective and objective methods. The establishment of the most probable etiology is based on clinical history (age of onset and rapidity of progression), hormone profile, and, in some cases, genetic analysis.

## Physical Examination

The quantification of hirsutism in women can be obtained through objective and subjective methods. Objective methods, such as photographic evaluations, weighing of shaved or plucked hairs and microscopic measurements are reliable. However, the complexity and high cost of these methods limit their use in clinical practice [29]. Subjective methods mainly refer to visually scoring terminal hairs in specified areas. These methods have the advantage of being easy, convenient, cheap, and fast; however, they are subject to some inter-observer variation. This limitation can be drastically reduced if the visual score is applied by trained physicians at least 3 months after the use of laser or electrolysis, at least 4 weeks after depilation or waxing, and at least 5 days after shaving, and if the number of examiners is minimized [29]. Of the visual scores available, the modified Ferriman–Gallwey score (mFG) has now become the gold-standard for the evaluation of hirsutism [30]. This method applies a similar 0–4 scale to nine body areas (upper lip, chin,

chest, upper and lower back, upper and lower abdomen, arm, forearm, thigh, and lower leg) that appear to be the best areas indicative of the action of androgens on the female hair follicle [29]. There are actually two open questions related to the interpretation of the mFG score. The first is the cutoff value to be used to diagnose the presence of hirsutism. The second is what interpretation to give to hirsutism predominantly localized on the face with respect to hirsutism predominantly localized on the trunk or arms, and what interpretation to give to the presence of terminal hairs selectively on the face in the absence of an mFG score indicative of hirsutism. The Androgen Excess and Polycystic Ovary Syndrome Society recently issued recommendations regarding the cutoff value of the mFG score to be applied. The Society recommends adapting the cutoff to the race and ethnicity of the population to which it is applied and, if this value is unavailable, using a cutoff value of 8 or above for White, Black and South-East Asian women, and a cutoff of 3 or above for Far-East Asian women [21]. Given the importance of the topic in both clinical practice and scientific research, how to define hirsutism requires more intensive research, possibly involving dermatologists and with the help of new technologies. In addition, other factors should be considered in defining cutoff points, including age (i.e., pediatric versus adult age) and, as reported above, how the presence of terminal hairs selectively on the face should be evaluated with respect to body hair. In fact, this often represents a major complaint in women with borderline hirsutism mFG scores, irrespective of age, social condition, and health problems.

The clinical evaluation of virilization is based on genital Prader Staging (Fig. 13.2) and anogenital distance (Fig. 13.1b) in newborns and on a complete physical examination (evaluation of the presence or absence of palpable gonads, measurement of phallus length, urethral opening identification, presence or absence of a vagina, presence or absence of clitoral hypertrophy) thereafter. When virilization is clinically suspected, the diagnosis usually needs to be confirmed by imaging such as abdominal/pelvic ultrasound, genitourethrogram, and, if necessary, MRI.



**Fig. 13.2** Prader stages of genital androgenization

### Hormone Profile

As previously mentioned, hirsutism and virilization are markers of excessive tissue exposure to androgen action, which results from the interaction between local androgen concentration and tissue sensitivity to androgens. Therefore, the diagnosis of hirsutism and virilization do not necessarily reflect high circulating androgen levels. This means that serum androgen measurements are often not sufficient to diagnose the presence of hirsutism or virilization, or to establish their severity, although they are extremely useful to define the etiology. However, the assay performance of the analytical methods used to measure androgens in the circulation has to be seriously taken into account for the correct interpretation of the results. The performance of modern immunoassay methods in terms of specificity and accuracy is poor, particularly for some androgens (17OH-progesterone, androstenedione, DHEA) and for low circulating concentrations, such as those enriched by testosterone in prepuberty and in the normal adult female range (<1 ng/mL) [31]. Liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) is an innovative technique displaying good precision, sensitivity, and high accuracy for measuring female androgen levels throughout all stages of life, with the advantages of the high throughput and the low cost required for the analysis [32, 33]. Therefore, it represents a convenient and reliable assay when androgen measurement in females is required,

provided that a reference normal range is determined in house, by using a carefully selected healthy non-hyperandrogenic control female population [21]. In addition, LC-MS/MS makes it possible to measure important steroids such as 11deoxycortisol, and deoxycorticosterone (DOC) that cannot be measured with immunoassay methods and that are triggers for the diagnosis of uncommon forms of CCAH and NCCAH. Due to the numerous advantages of this technique, LC-MS/MS has recently been introduced in laboratories in critical fields that strongly rely on the reliability and rapidity of the measurement, such as newborn screening for congenital diseases including CCAH [34].

### Genetic Analysis

Genetic analyses are warranted when NCCAH or CCAH are strongly suspected as causes of hirsutism or virilization, because they are genetic disorders with autosomal recessive inheritance. The genes involved in all defects have been isolated and characterized, and specific mutations have been identified (Table 13.2). Genetic analysis for identification of mutations of the genes involved is informative for the index case (type and severity of the disorder) and for future prenatal diagnosis.

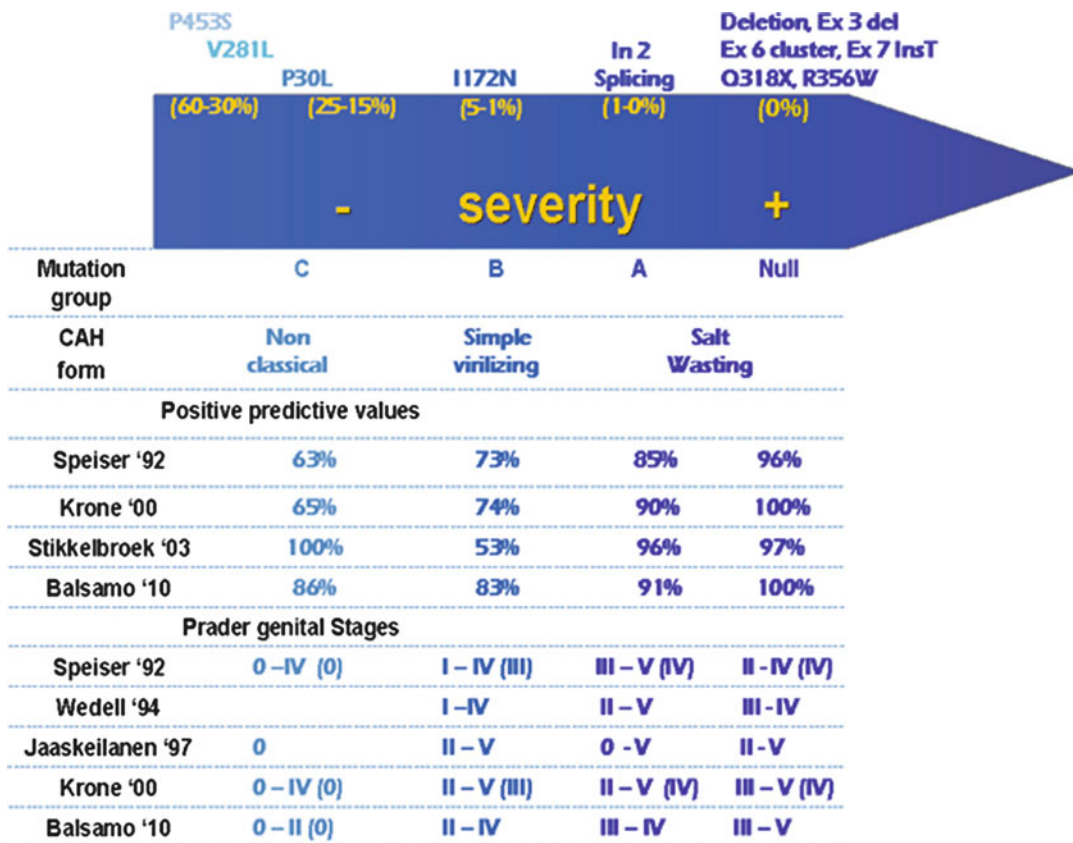
21-Hydroxylase deficiency, the most frequent cause of NCCAH and CCAH, is caused by cytochrome P450c21 enzyme impairment.

**Table 13.2** Genes involved in congenital adrenal hyperplasia (CAH) (modified from Ref. [32])

<i>Gene/protein type</i>	Chromosome location	Inheritance	Gonads	Müllerian structures	External genitalia	Other associated features
<i>HSD3B2/enzyme</i>	1p13.1	AR	Ovary	Yes	Female or ambiguous	CAH, adrenal insufficiency
<i>CYP21A2/enzyme</i>	6p21.23	AR	Ovary	Yes	Female, ambiguous or male	CAH, +/- adrenal insufficiency
<i>CYP11B1/enzyme</i>	8q21.22	AR	Ovary	Yes	Female, ambiguous or male	CAH, +/- hypertension
<i>POR/CYP electron donor</i>	7q11.2	AR	Ovary	Yes	Female or ambiguous	Mixed features of 21-OHDef, 17-OHDef/17-20-lyaseDef, aromatase Def; +/- Antley-Bixler's Syndrome
<i>CYP19/enzyme</i>	15q21	AR	Ovary	Yes	Ambiguous	Maternal virilization during pregnancy, absent breast development at puberty, except partial cases

The *CYP21A2* gene, encoding for 21-hydroxylase, is homologous at 98 % in exons and at 96 % in introns to the non-functional *CYP21A1P* pseudogene. The high degree of sequence homology and tandem repeating order of RCCX module sequences is the cause of sequence misalignments during meiosis, which result in frequent unequal meiotic crossovers, as these modules are located in the HLA region of the genome (where recombination events occur at a particularly high level to ensure high immunological diversity) [35]. This mechanism generates gene deletions as well as the commonly called “large gene conversions”, both consisting in chromosomes with a chimeric gene (with a 5' part of pseudogenic origin fused with a 3' *CYP21A2* region), but without a *CYP21A2* gene [36]. The majority of disease-causing mutations are small mutations that arise from micro-conversions (transfer of small DNA sequences) from *CYP21A1P* to *CYP21A2*: P30L, IVS2-13A/C>G (I2 splice), Del 8 bp E3, I172N, Cluster E6, V281L, 1762\_1763insT (L307 Frameshift), Q318X, R356W; the P453S mutation, which is not pseudogene-derived, is usually added to this list. The remaining 10 % of alleles have new/rare mutations due to random events [37]; over 90 rare pseudogene-independent

mutations are actually listed in the Human Cytochrome P450 (*CYP*) Allele Nomenclature Committee at <http://www.imm.ki.se/CYPalleles/cyp21.htm>. The phenotype derives from the type/types of genetic mutations with a final influence on the total residual enzymatic activity [38] (Fig. 13.3). The CCAH forms result from deletions/conversions or point mutations associated with <10 % residual enzymatic activity (Null, A, B mutation groups of Fig. 13.3); the NCCAH forms result from point mutations with residual enzymatic activity comprised between 15 and 60 % (C mutation groups of Fig. 13.3). As for genital appearance, while the presence of “group C” mutations is highly predictive of forms without external genital virilization, a clear predicting capacity does not exist for stages of virilization within the Null, A and B mutation groups. In fact, although more severe virilization tends somehow to be present in patients with the most severe genotypes [39], Prader stages from II to V have, however, been reported in each of the previous mutation groups [40] (Fig. 13.3). When patients are compound heterozygotes, with two or more different mutations on the two alleles, the severity of the phenotype depends principally on the mutation with the less impaired residual activity [38].



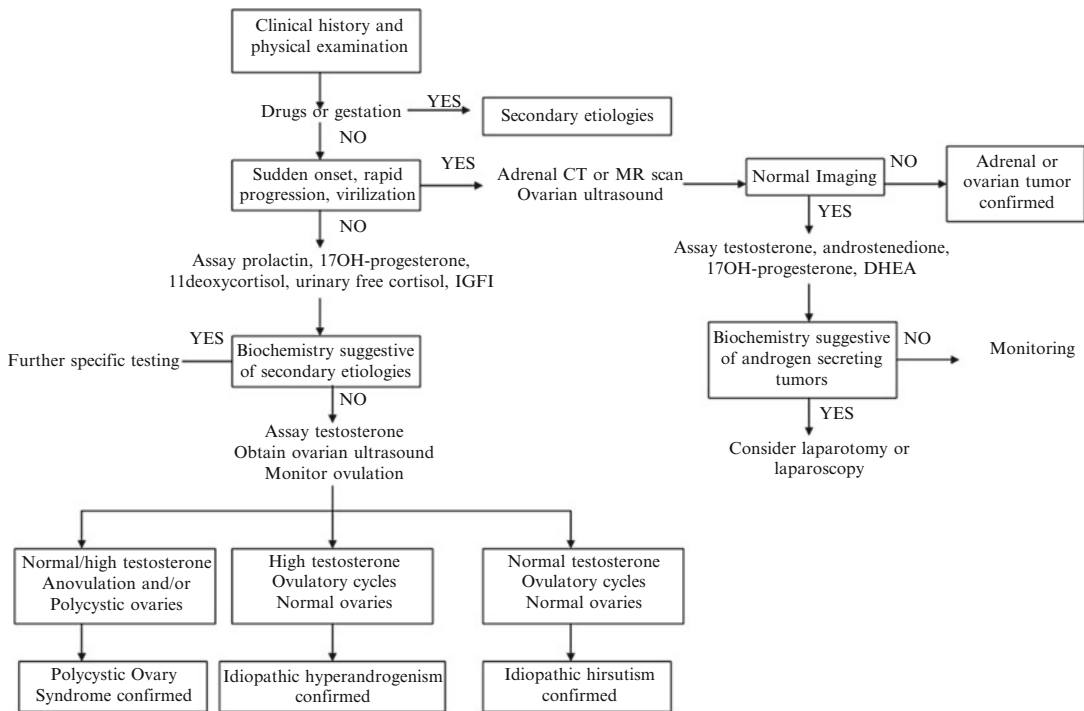
**Fig. 13.3** CYP21A2P derived mutations: phenotypic spectrum (modified from Ref. [35, 40])

### Differential Diagnosis

Hirsutism is a marker of excessive tissue exposure to androgens and, therefore, always deserves to be investigated. Various disorders enter into the differential diagnosis, some more frequent (PCOS, idiopathic hirsutism, idiopathic hyperandrogenism), others more rare (NCCAH due to 21 hydroxylase deficiency, hyperprolactinemia, hypothyroidism, drugs, gestation), others very occasional (androgen secreting tumors, Cushing’s syndrome, acromegaly, NCCAH not due to 21 hydroxylase deficiency, CCAH). However, all these causes must be taken into account in the correct approach to a patient who complains of hirsutism. In addition, a correct medical approach to hirsutism assumes the need to exclude whether it accompanies signs of virilization or, alternatively, it is isolated. A diagnostic algorithm is

suggested in Fig. 13.4. All patients presenting with hirsutism should be firstly subjected to a careful evaluation of the clinical history and a thorough physical examination. Age of onset and rapidity of progression are key factors that should often be investigated. Functional causes or NCCAH, in fact, almost always show a peripubertal onset and a slow progression over years and are generally not associated with signs of virilization. In contrast, androgen secreting tumors usually manifest at any age with sudden onset and rapid progression and are usually associated with signs of virilization. Clinical screening is also essential to rule out secondary forms of hirsutism or virilization that, however, usually need serum or urine measurements of the relevant hormones and, if necessary, specific testing in order to be confirmed. Functional forms of hirsutism (PCOS, idiopathic hirsutism, idiopathic hyperandrogenism) must be considered and dealt with only after





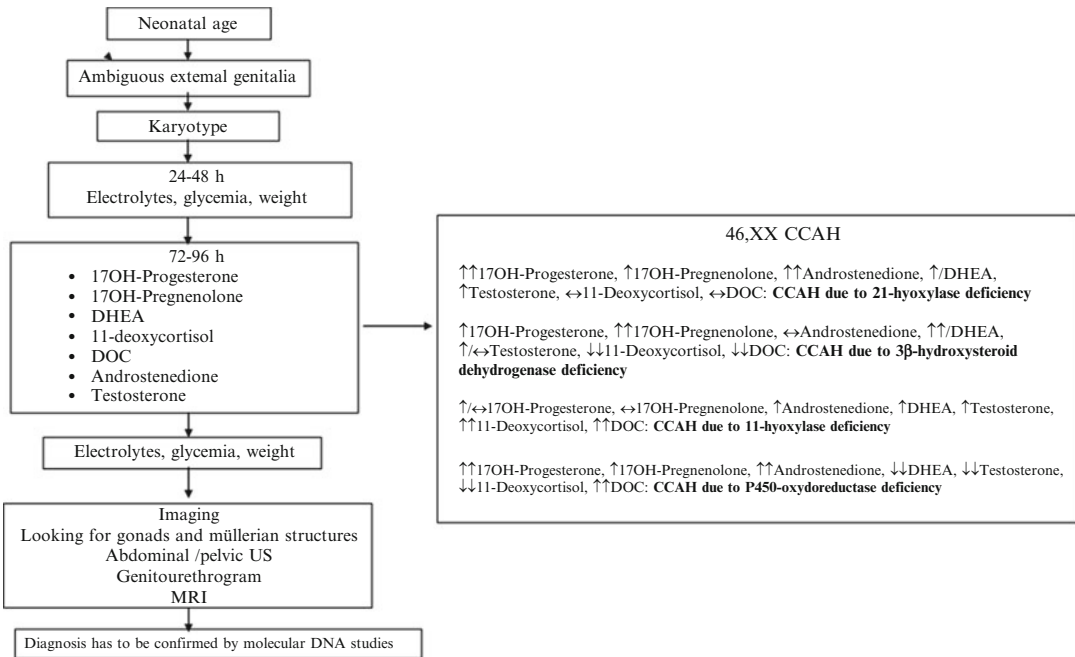
**Fig. 13.4** Diagnostic algorithm for hirsutism and virilization

androgen secreting tumors and the other forms have been excluded. At this point, measurement of testosterone in serum, assessment of ovulatory function and ovarian ultrasound evaluation are essential for the differential diagnosis between the three forms. CCAH is generally diagnosed in neonatal age because of external ambiguous genitalia, salt losing crisis, or, rarely, hypertension (Fig. 13.5). CCAH due to 21-hydroxylase deficiency is the commonest cause of ambiguous genitalia of the newborn. Ambiguous genitalia at neonatal age may depend more rarely on 11-hydroxylase,  $3\beta$ -hydroxysteroid dehydrogenase, and P450-oxidoreductase deficiencies [10, 41]. All these forms of CCAH are generally characterized by varying degrees of genital virilization (Prader staging, Fig. 13.2) possibly accompanied by genital pigmentation (expression of excessive ACTH production). Salt losing crisis may be associated with 21-hydroxylase and  $3\beta$ -hydroxysteroid dehydrogenase deficiencies [10, 42]. Hypertension due to DOC excess is extremely rare in newborns affected by

11-hydroxylase deficiency. Measurement of 17OH-progesterone, 17OH-pregnenolone, androstenedione, DHEA, testosterone, 11-deoxycortisol, and DOC in the circulation is essential for a differential diagnosis of the various causes of virilizing 46,XX CCAH (Fig. 13.5).

## Management of Hirsutism and of Virilization

Hirsutism is a clinical sign and not a disease by itself. Therefore, its presence does not necessarily require treatment. Physicians should decide whether hirsutism is to be treated or not by evaluating not only the severity of the phenomenon but also the subjective perception of the patient that does not necessarily correspond to the true extent of hair growth. The correct management of hirsutism is, obviously, the treatment of the underlying cause, if possible. Usually, however, treatment targeted at ameliorating hirsutism directly is also necessary.

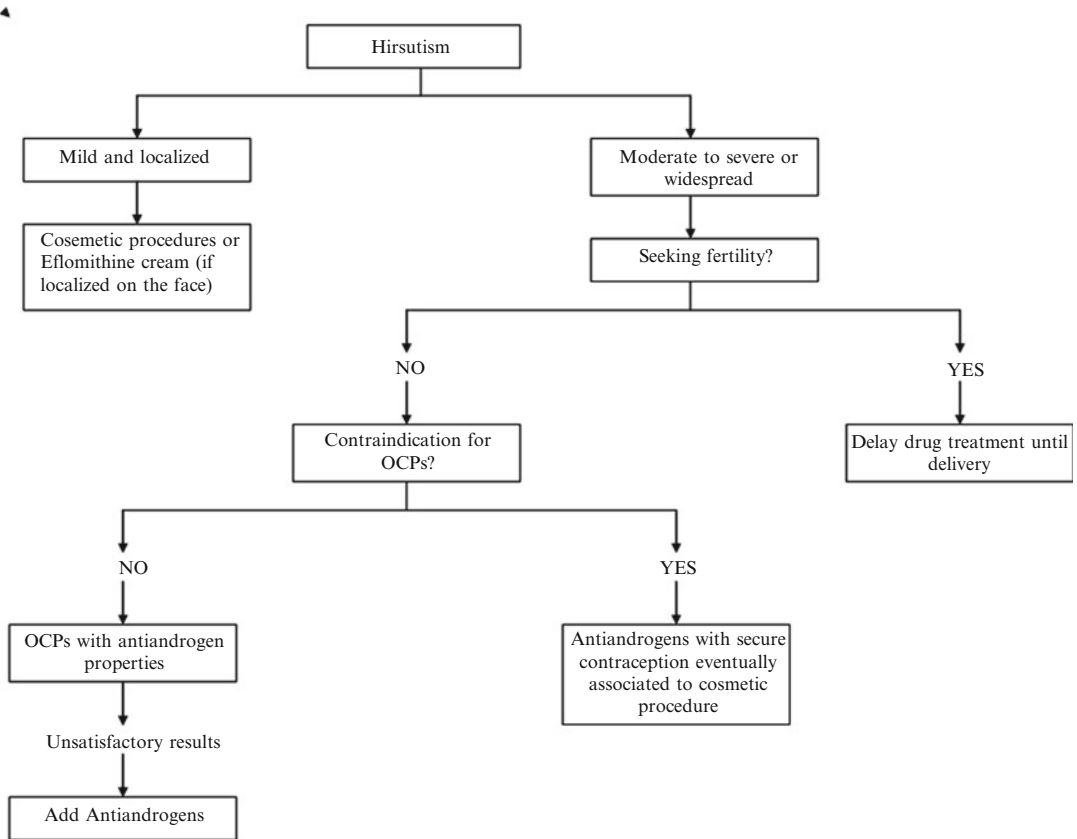


**Fig. 13.5** Diagnostic algorithm for an early diagnosis of virilization in newborns

Cosmetic measures are effective as individual therapy in controlling mild and localized hirsutism. In addition, they are recommended as an adjuvant to pharmacological therapy in cases of clinically moderate to severe hirsutism. Among the cosmetic measures available, only electrolysis and the newer methods, such as laser therapy and intense pulse light, may result in permanent amelioration of hirsutism in the treated area [43, 44].

In cases of mild hirsutism localized on the face, an alternative to the cosmetic approach is the topical application of a 13.9 % eflornithine cream [45]. Eflornithine is an irreversible inhibitor of L-ornithine decarboxylase, an enzyme that catalyzes the conversion of ornithine to putrescine, a polyamine that is critical to the regulation of cell growth and differentiation within the hair follicle [45]. Recent studies demonstrate that continuous topical administration of eflornithine cream reversibly slows facial hair growth in up to 70 % of patients treated [46]. Unfortunately, good success with this procedure is relatively uncommon and local side effects need to be carefully considered.

A systemic pharmacological approach is usually required when hirsutism is moderate to severe and/or it is widespread. Drugs that are safer and more cost-effective are oral contraceptive pills (OCPs). Their efficacy is mainly justified by the ability of progestin to suppress luteinizing hormone levels and thus ovarian androgen production, and by the ability of estrogen (ethinyl-estradiol-EE) to increase sex hormone binding globulin (SHBG), thus reducing bioavailable free androgens [47]. Moreover, OCPs induce a moderate reduction of adrenal androgens, probably through a direct interaction with adrenal steroid synthesis [48]. In addition to these effects, which are common to all OCPs, some progestins have anti androgenic properties, due to their antagonizing effects on the androgen receptor (cyproterone acetate, drospirenone, dienogest) and to the inhibition of 5 $\alpha$ -reductase activity [cyproterone acetate, clormadinone acetate, “third-generation” progestins (desogestrel, gestodene, norgestimate), drospirenone, and dienogest] [47]. Although all OCPs are efficacious in reducing hirsutism, OCPs containing a



**Fig. 13.6** Algorithm for the management of hirsutism

progestin with antiandrogen properties are preferable for the treatment of hirsutism [49, 50].

In cases of moderate to severe forms of hirsutism not responsive to OCPs or, alternatively, when OCPs are contraindicated, the use of antiandrogens alone or combined with OCPs is indicated. Antiandrogens (androgen receptor blockers—flutamide, spironolactone—and 5 $\alpha$  reductase inhibitors—finasteride, spironolactone) are, in fact, the most effective drugs for hirsutism currently available [51]. At present there is not enough information to establish a scale of efficacy for these drugs. Some comparative studies did not find significant differences in efficacy between antiandrogens, whereas in other studies flutamide appeared to have the greatest efficacy, and finasteride the lowest [22]. Furthermore, these drugs do not appear to extend dose-dependent effects against hirsutism [22].

Therefore, the minimum effective dose is recommended, in order to reduce the side effects. It must be stressed that antiandrogens cannot be given to pregnant women for the risk of feminization of male fetuses and should only be prescribed to women using secure contraception. An algorithm for the management of hirsutism is suggested in Fig. 13.6.

Conversely, virilization always deserves treatment, with an approach that may be medical and/or surgical depending upon the underlying disorder. Surgery is the treatment of choice for all patients with hormone-secreting adrenal or ovarian tumors [52, 53] and for those patients with virilization due to pituitary adenomas secreting ACTH, GH, or prolactin, if indicated.

CCAH always needs glucocorticoid treatment (associated with mineralocorticoid supplementation in the salt wasting forms) and surgical

correction of virilization. Standard treatment at diagnosis until growth is complete is hydrocortisone at 10–20 mg/m<sup>2</sup>/day, possibly divided into three doses, orally. Sometimes, in sick infants, 2 mg/kg of hydrocortisone hemisuccinate by i.v. bolus, followed by 20–30 mg/m<sup>2</sup>/day by constant i.v. infusion, may be a more appropriate initial treatment. After growth is complete, other more potent synthetic glucocorticoids may be used in a double (prednisone, prednisolone: hydrocortisone equivalent dose=5) or a single (dexamethasone: hydrocortisone equivalent dose=70) administration. Blood electrolytes need monitoring daily from day 3 of life and if K<sup>+</sup> rises or Na<sup>+</sup> falls (salt loss occurs most frequently between day 6 and 21 of life) 9 $\alpha$ -fludrocortisone should be started at 0.05–0.2 mg/day in two divided doses. Salt supplementation (5 mEq/kg/day; NaCl=1 g=17 mEq) is a fundamental complement to mineralocorticoid treatment, at least in the first 6 months of life. Significant controversy exists on the timing of feminizing genitoplasty in girls with virilizing CCAH. When possible, feminizing genitoplasty should be a one-stage repair using the newest techniques. Clitoroplasty should only be considered in cases of severe virilization (Prader III–V) with prominence for functional outcome rather than cosmetic appearance. Vaginoplasty should be performed in infancy only if the persistence of a urogenital sinus causes complications. Surgical improvement generally needs to be done at puberty. Vaginal dilation is not recommended in childhood, while during young adulthood it may be useful to avoid the need for bowel vaginoplasty [27].

In families at risk for a virilized female newborn (index case affected by classic 21-hydroxylase or 11-hydroxylase deficiencies), prenatal diagnosis and treatment may be undertaken. Early administration (before 8 weeks of gestational age) of dexamethasone to the mother (20  $\mu$ g/kg/pre-pregnancy), in fact, is able to prevent genital virilization in most affected females. Treatment should be started in all pregnancies at risk for virilized female newborn until chorionic villous sampling for sex and genetic analyses can be performed (10–11 weeks of gestational age).

Thereafter, only affected female fetuses need to continue the treatment throughout pregnancy. To reduce the number of fetuses exposed to dexamethasone unnecessarily, PCRs for cell-free Y DNA in maternal blood at 5–6 weeks of gestation for prenatal sexing screening is now available as an experimental technique [54, 55]. In any case, due to possible maternal side effects (Cushing's syndrome) and the lack of long-term trials for its safety, antenatal dexamethasone treatment should only be carried out in specialized centers with the use of approved protocols [56].

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## Epidemiology

Although the average age at menopause is 51 years, in 5 % of women it occurs after 55 years of age, which is considered late menopause, and in 5 % between 40 and 45 years, which defines premature menopause. The cessation of cycles that occurs before the age of 40 is considered premature ovarian failure [1].

Various factors are considered as determinants of age at menopause. Thirteen common genetic variants located on chromosomes 5, 6, 19, and 20, related to age at menopause were identified [2]. Genetic variation in the estrogen receptor gene may be another determining factor, as well as permutations in the FMR1 gene that defines fragile X syndrome and causes premature ovarian failure [3].

Women with a family history of early menopause are at increased risk of developing amenorrhea earlier on. Women whose mothers started the phase of menopause at a young age have a

sixfold greater likelihood of early menopause [4]. Race and ethnicity may also affect age at menopause. In two prospective, multiethnic studies, natural menopause occurred earlier among Hispanic women and later on in Americans and Japanese, when compared with a Caucasian population [5].

Smoking reduces age at menopause by about 2 years [6]. A study of 10,606 middle-aged women showed that 31 % of female smokers developed natural menopause earlier than non-smokers [7]. Other factors also seem to be involved, such as the consumption of galactose, a history of type 1 diabetes, intrauterine exposure to diethylstilbestrol, and nulliparity [2, 8].

Hormonal changes begin years before the menopause. In the final years of reproductive life menstrual cycles are ovulatory, but gradually, the duration of the follicular phase begins to decrease. In the initial transition to menopause, women experience some menstrual irregularity and in this phase inhibin B concentrations begin to fall due to a decline in the number of ovarian follicles, where as FSH levels begin to rise with a relative maintenance of estradiol levels, but with low concentrations of progesterone [9].

In late transition there is an increase in the variability of the cycle, with fluctuations in serum levels of FSH and estradiol. Following menopause, when there is a total loss of ovarian follicles, the ovary can no longer synthesize estradiol, but keep producing and secreting the androgenic hormones under the stimulus of luteinizing hormone (LH) [10].

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After 12 months of amenorrhea in a woman aged over 45 years and in the absence of other physiological or pathological causes, we identify the presence of menopause [3, 5].

## Clinical Manifestations

Clinically women experience drastic changes in the body (Table 14.1). Chronic anovulation and progesterone deficiency can lead to long periods of uterine exposure to estrogen, thereby generating anovulatory bleeding and endometrial hyperplasia. Hot flashes, which are manifested in 75 % of women, are the most common acute change during menopause. They are self-limited, with an average duration of 5 years, begin suddenly, and are characterized by a feeling of warmth in the face and chest that spreads rapidly. The heat sensation lasts about 2–4 min and is associated with intense sweating, palpitations and anxiety. It occurs predominantly at night, causing severe sleep disturbances [5].

As the epithelia of the vagina and urethra are sensitive to the action of estrogen, its thinning occurs during menopause, resulting in vaginal atrophy and related symptoms, such as vaginal dryness, vaginitis, itching and pain during intercourse, and urethral atrophy, causing greater susceptibility to infections and urinary incontinence [11].

Sexual dysfunctions are highly prevalent in this period. Estradiol deficiency significantly reduces blood flow to the vagina and vulva, resulting in decreased vaginal lubrication and pudendal nerve neuropathy [12]. Vaginal dryness and dyspareunia, as previously mentioned, may contribute to decreased sexual function in this period [13].

**Table 14.1** Prevalence of menopausal symptoms [11]

Symptoms	Prevalence
Hot flashes	80–90 %
Sleep disturbance	38–46 %
Depression	50 %
Dementia	Uncertain
Vaginal dryness	21–47 %
Cognitive changes	Uncertain
Joint pain	Uncertain
Skin changes	Uncertain
Breast pain	Uncertain

Studies investigating the relationship between menopause and depression present conflicting findings. Some longitudinal studies have found no association. However, several others have shown a significant association between the menopausal transition and depression [14]. The largest prospective study to date, the Study of Women's Health Across the Nation (SWAN) trial, reported that perimenopausal women showed a higher rate of depressive symptoms (14.9–18.4 %) than premenopausal women (8–12 %), the most common symptoms being irritability, nervousness, and emotional lability [15].

Other, less common, symptoms are breast tenderness, headache, skin aging, and joint pain [16].

## Diagnosis

Menopause is clinically defined as a period of 12 months of amenorrhea in a woman over 45 years of age, in the absence of other biological or physiological cause. The best approach to the diagnosis of perimenopause is a longitudinal evaluation of the history of the menstrual cycle and menopausal symptoms (vasomotor waves, mood swings, sleep disturbances). There is no need for measurement of serum FSH, estradiol, or inhibin levels for diagnostic purposes.

Some medical conditions can mimic conditions of menopause, such as hyperthyroidism, which should always be considered in the differential diagnosis, and occur together with irregular menstruation, sweats (although different from typical hot flashes) and mood changes. Other causes for menstrual cycle changes should be considered, including pregnancy, hyperprolactinemia, and other thyroid diseases. Atypical hot flashes and night sweats may be present in other disorders, such as drug use, pheochromocytoma, carcinoid tumors, or other malignancies [17].

## Hormone Therapy

Hormone therapy (HT) in postmenopausal women is currently recommended for use in short-term treatment of moderate to severe vasomotor symptoms. Long-term use for primary or



secondary prevention of cardiovascular disease and osteoporosis is no longer recommended [18].

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## Vasomotor Symptoms

Hormone therapy, estrogen with or without progesterone, remains the gold standard treatment for the relief of menopausal vasomotor symptoms and their consequences. It is therefore a reasonable option for most postmenopausal women, except those with a history of breast cancer, coronary heart disease, previous thromboembolic event or stroke, or those at high risk for these complications. In healthy women, the absolute risk of an adverse event is extremely low [18]. The exclusive use of progesterone also reduces vasomotor symptoms, but less efficiently than estrogen therapy [19].

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## Genitourinary Tract

Both vaginal and urethral epithelia are sensitive to estrogen, and estrogen deficiency leads to their thinning, resulting in vaginal atrophy, which may generate symptoms of vaginal dryness, itching, and often dyspareunia. Both systemic and local estrogen therapy are effective for symptoms of genitourinary atrophy. Vaginal administration (available as creams, tablets, or rings) is an extremely effective therapy, making it an excellent choice for nearly all postmenopausal women (with the exception of patients with breast cancer) and can be administered in the long term, since systemic absorption is minimal [18].

Local estrogen therapy may benefit some women with an overactive bladder. A clinical study demonstrated that using an estradiol ring showed clinical efficacy similar to the use of oxybutynin in women suffering from an overactive bladder [20]. The use of low-dose transdermal estradiol, however, did not affect the development of urinary incontinence [21]. A recent clinical trial reported an increased risk of nephrolithiasis in healthy women on hormone therapy, but the mechanisms involved have not been elucidated [22]. Two studies

have shown a reduced risk of recurrent urinary tract infection in women using vaginal estrogen therapy [23, 24].

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## Sexual Function

Hormone therapy is not recommended for the treatment of sexual dysfunction, including decreased libido [18]. There is no evidence that estrogen therapy acts independently in sexual interest, arousal, and orgasmic response. Low doses of local estrogen can improve sexual function merely by increasing local blood flow and vaginal lubrication [25].

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## Quality of Life

Although there is no approval for the use of hormone therapy for the sole purpose of improving the quality of life of women, data shows that symptomatic women show an improvement in some areas of quality of life through relief of vasomotor symptoms. There is no evidence to support this improvement in asymptomatic women [18].

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## Osteoporosis

Some randomized controlled trials and those controlled with placebo support the use of estrogen therapy for the prevention of osteoporosis and fractures, including hip fractures and treatment of proven osteoporosis [18]. However, to date, there has been no approval for their use in the treatment of osteoporosis in postmenopausal women without vasomotor symptoms.

The results of the WHI trials indicated some benefits with hormone therapy. Women randomly assigned to estrogen and progesterone had a 34 % reduction in the risk of vertebral and hip fractures (hip, 6 fewer per 10,000 woman-years; vertebral, 6 fewer per 10,000 woman-years; and total, 46 fewer per 10,000 woman years) and fewer cases of diabetes (15 fewer per 10,000 woman-years) than those randomly assigned to placebo [26].

Women randomly assigned to estrogen alone had fewer fractures (hip, 7 fewer per 10,000 woman-years; vertebral, 6 fewer per 10,000 woman-years; and total, 56 fewer per 10,000 woman-years) and fewer cases of invasive breast cancer (8 fewer per 10,000 woman-years) and breast cancer deaths (2 fewer per 10,000 woman-years). Whereas fractures were a major predefined secondary outcome and were determined by clinical and radiographic criteria, diabetes was diagnosed on the basis of a less rigorous approach using post hoc analysis of self-reports [26].

When there are failures or adverse effects of standard therapy for osteoporosis, prolonged use of hormone therapy is an option for women at high risk of osteoporotic fractures. However, its beneficial effects on bone mass and fracture reduction are minimized quickly after its administration has been discontinued [27].

In women who experience premature menopause, unless there are contraindications, hormone therapy should be used for the purpose of bone loss prevention, rather than the standard therapy for osteoporosis, until they reach the age of menopause, when the treatment should be reevaluated [18].

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## Cardiovascular Effect

Based on extensive observational data, it was believed that estrogen exerted a cardioprotective effect, and as a result, estrogen therapy was routinely prescribed for primary and secondary prevention of cardiovascular disease (CVD). However, data from the Heart and Estrogen/Progestin Replacement Study (HERS I and II), other small controlled trials and two meta-analyses have not confirmed this protective effect on the heart [28–30].

In 2002, the subgroup of women in the WHI who used the estrogen–progestin combination showed an increased risk of coronary heart disease and breast cancer, and the study was discontinued prematurely. The results of the subgroup that used only estrogen therapy, published in 2004, showed a tendency to a decreased risk of breast cancer, but an increased risk of stroke and

thromboembolic disease, and no benefits on coronary heart disease [18, 26].

Some, but not all observational studies suggest that long-term hormonal therapy is associated with a smaller accumulation of calcium in the coronary arteries, data which is strongly correlated with the presence of atheromatous plaques and the risk of future coronary events [31].

The HERS I study demonstrated a twofold to threefold increase in the risk of venous thrombosis and pulmonary embolism with hormone therapy. However, the absolute risk was low, ranging from one case to two or three cases per 100,000 women. The data is related to the oral use of the hormone. The HERS II study found a 2.89 times risk of thromboembolism in users of combined hormone therapy, estrogen/progesterone, compared with the placebo and a trend toward an increased risk of pulmonary embolism. The WHI trial found a risk twice higher of pulmonary embolism in users of combined hormone therapy, representing eight more cases of pulmonary embolism in 10,000 women/year. This risk was attributed to the combination of estrogen and progestin [18, 26]. There is no data for other, non-oral forms of administration of hormonal therapy.

The WHI showed an increase in the risk of stroke, but no effect on hemorrhaging. When all women in that trial were analyzed, there were 8 additional cases of stroke per 10,000 women/year in combined therapy and 11 cases per 10,000 women/year in estrogen-alone therapy, and in both, the risk was eliminated after discontinuation of treatment [26]. In a recent data analysis from the WHI trial involving only women aged 50–59 years, there was no significant effect on the risk of stroke [32]. The risk of stroke did not significantly increase in the HERS I and II studies [33, 34]. The data from observational studies on the association between hormone therapy and stroke have been inconsistent. Various studies have indicated a positive association, but others showed no effect on the risk of stroke [18].

One difference between observational studies and the WHI study is the fact that the women enrolled in the latter presented an average age of 63 years at the start of the use of hormone

therapy, about 12 years after menopause had begun [18, 26]. Participants in the observational studies began therapy immediately after the beginning of menopause, with a mean age of 51 years. That is, women from the WHI were older and began using the hormone later, which is unusual in clinical practice. As the atherosclerotic lesions develop early, it is likely that the WHI participants already presented sub-clinical coronary disease, and therefore would not be candidates for hormonal regime, since hormonal therapy appears to be more effective in primary prevention than in secondary prevention. The idea that differences in age or time since menopause at the start of hormone therapy are responsible for differences in cardiovascular outcomes has become known as the “window of opportunity” [35].

In the observational studies and in animal models that suggested beneficial cardiovascular effects of hormone therapy, the subjects generally initiated therapy at the time of menopause (often for management of vasomotor symptoms), or in animal studies, treatment began immediately after ovariectomy. This contrast with the WHI, in which treatment was initiated more than a decade after menopause in most study participants, led to the development of the “window of opportunity.” This theory proposed that initiation of HT at or shortly after menopause is cardioprotective, whereas starting treatment at a time remote from menopause may be harmful. Indeed, in the WHI, the trend toward lower rates of CVD events was noted in women who were within 10 years of menopause or who were aged 50–59 years at the time of entry into the trial. In the estrogen and progestin arm, women within 10 years of the menopausal transition had a hazard ratio (HR) of coronary heart disease (CHD) events of 0.89, compared with 1.71 in those more than 20 years from menopausal transition. In the conjugated equine estrogen (CEE) alone arm, those aged 50–59 years had an HR of 0.56, compared with older women, whose HR was almost 1.0 [35].

In addition, women enrolled in the CEE arm and aged 50–59 at baseline had coronary calcium measured by computed tomography; women who

received CEE had significantly lower scores at trial completion than those who received placebo [31]. In this young population, the incidence of coronary events was low, and the absolute risk of clinical CHD events was small. In a more recent analysis, the results were examined after pooling the data from the WHI estrogen-alone and estrogen and progestin trials [35]. Women enrolled within 10 years of the onset of menopause had a HR for CHD of 0.76 (CI, 0.50–1.16). The HR continued to rise with years since menopause. Initiating therapy from 10 to 19 years after menopause gave a HR of 1.10 (CI, 0.84–1.45), and when initiated after 20 or more years, the HR was 1.28 (CI, 1.03–1.58). The P value for the trend was 0.02, supporting the timing hypothesis, which predicts that protection from atherosclerosis is evident only when hormone therapy is initiated shortly prior to the onset of menopause and before the development of advanced atherosclerotic plaques.

The timing hypothesis is further supported by several recent studies. A Bayesian meta-analysis of hormone therapy mortality in younger postmenopausal women (mean age, 55 years) presented the combined results of 19 randomized clinical trials that enrolled 16,000 women at a mean age of 55 years, totaling 83,000 patient-years. This study showed a relative risk of mortality of 0.73 [18]. The analysis also demonstrated a cardiovascular benefit when HT was initiated early, supporting the timing hypothesis. Current ongoing prospective randomized trials will formally test this hypothesis.

Despite this reassuring data, HT in postmenopausal women is still indicated only for the management of vasomotor symptoms, since there is no data to support its use in primary or secondary prevention of coronary disease. An ongoing primary prevention trial, Kronos Early Estrogen Prevention Study (KEEPS), will evaluate whether early initiation of HT reduces the risk of coronary heart disease through intermediate risk markers such as measures of the intima-media layer and accumulation of calcium in coronary arteries [36]. Another ongoing study, Early versus Late Intervention Trial with Estradiol (ELITE), will assess the appearance or progression of atherosclerosis,

through ultrasound measurement of wall thickness in the carotid artery and CT evaluation of the coronary calcification index in early postmenopausal women and in women in late menopause [18, 35].

Another topic of constant debate is the role of the mode of administration of the hormone in relation to the adverse effects observed in large studies. The oral route is associated with an increase in thrombotic effects and decreased synthesis of thrombolytic factors in the liver, induced by the hepatic first-pass of estradiol, which could justify a two- to three-fold increase in the risk of thromboembolism observed with the use of oral, but not transdermal estrogen [18, 37]. Low-dose, cyclic, and transdermal formulations have been suggested as potentially favorable alternatives. Unfortunately, no large, prospective, randomized trials exist that carefully compare these alternative regimens. In the KEEPS trial, a transdermal regimen is being directly compared with an oral regimen to determine whether both have an equivalent effect on the progression of atherosclerosis [35].

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## Diabetes Mellitus

Large clinical trials have shown that hormone therapy reduces the appearance of type 2 diabetes mellitus (T2DM), despite not having been approved as a prevention measure in this disease. Women in the WHI and HERS studies who received estrogen/progesterone showed an average reduction of 21 % in the incidence of T2DM [38].

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## Endometrial Cancer

Women constantly exposed to endogenous or exogenous estrogens not neutralized by progesterone are at increased risk of developing hyperplasia and endometrial cancer. The risk of endometrial cancer is six to eight times higher in women using estrogen compared with women who do not use it [39].

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## Breast Cancer

The relationship between breast cancer and hormone therapy is complex. There are dozens of observational, case-control and cohort studies, with results which are not very consistent. A meta-analysis of observational studies, carried out in 1997, summed up 90 % of the literature (53,705 women with breast cancer, compared with 108,411 controls) and showed that each year of hormone therapy confers a relative risk for breast cancer of 2.3 %, attributable to the use of progesterone [40].

Despite demonstrating an increased incidence, the present study, like others, showed no increase in mortality from the disease. The group of women using estrogen/progestin in the WHI study was discontinued because of the 26 % increase in the risk of breast cancer. That is, for every 10,000 women, 38 developed breast cancer, while among nonusers of hormone therapy, 30 cases of breast cancer in 10,000 women were found [26].

Studies have not clarified whether the risk of breast cancer differs between continuous or intermittent use of progesterone, with observational studies suggesting that the risk may be greater with the continuous use of this drug. It is also unclear whether there is a class effect of progesterone or if a specific agent influences a higher risk of breast cancer. Data from a large observational study suggests that hormone therapy with micronized progesterone carries a low risk of breast cancer with short-term use, but generates an increased risk if used for long periods [41].

It is known that combination therapy and, to a lesser extent, estrogen-alone therapy promote increased proliferation of breast cells, breast tenderness, and increased mammographic density, complicating the interpretation of mammography and delaying the diagnosis of breast cancer [18].

In The Million Women Study (MWS) researchers reported an increased risk of breast cancer in women who start hormone therapy soon after menopause [42]. Women in the WHI study who used estrogen alone had no increased risk of developing breast cancer after an average of 7.1 years of

use, and there was even a decrease in the risk in this arm of the study, despite having shown an increase in risk early in treatment. It is claimed that the hypothesis that justifies this reduction in risk is the probable apoptotic effect exerted by estrogen on neoplastic mammary cells in an environment with low levels of estrogen [18]. This finding was not demonstrated in the MWS study [42].

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## Ovarian Cancer

The association between hormone therapy and ovarian cancer is unclear. A cohort study of 44,241 postmenopausal women concluded that women who used estrogen alone as hormone therapy for more than 10 years had a significant risk of developing ovarian cancer, while those who used combined therapy for a short period showed no increased risk [43]. According to data from the MWS, women using hormone therapy are at increased risk for ovarian cancer [44]. Another observational study found a strong association between estrogen and death due to ovarian cancer. Moreover, the risk is increased in women who used estrogen for 10 years or more [18].

In a post hoc analysis of the arm of WHI using combination therapy for an average of 7.1 years, the incidence of non-small cell lung cancer did not increase significantly; there was, however, a significant increase in the number of deaths from this cancer, as well as the presence of metastatic and poorly differentiated tumors. This association was found exclusively in women over 60 years who were smokers or who had a history of smoking. The arm that used only estrogen therapy exhibited no increase in incidence or mortality from lung cancer [45].

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## Cognition and Dementia

Randomized controlled studies of short duration, comparing estrogen with placebo show inconsistent results. The methodology, the type of estrogen, age, the type of menopause (natural or surgical), and, in particular, the tests performed are different. Some studies show benefits in some tests, focused mainly on memory and verbal

fluency in patients using estrogen [18]. A meta-analysis concluded that the evidence is still scanty and inconsistent and does not explain the improvement in symptoms and relief from depression, indicating the need to evaluate the various types of hormone therapy used [46].

WHIMS reported hormone therapy (HT), conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA), increased the risk for dementia [HR 1.76 (95 % CI, 1.19–2.60);  $P=0.005$ ] and global cognitive decline, with a mean decrement relative to placebo of 0.21 points on the Modified Mini Mental State Examination in women age 65 and older. A subset of WHIMS participants joined the ancillary WHI Study of Cognitive Aging (WHISCA) trials, in which domain-specific cognitive tests and mood were measured annually. Compared with placebo, CEE+MPA had a negative impact on verbal memory over time and CEE-Alone was associated with lower spatial rotational ability at the initial assessment, but the difference diminished over time. The ancillary WHIMS-MRI study measured subclinical cerebrovascular disease to possibly explain the negative cognitive findings reported by WHIMS and the increased clinical stroke in older women reported by the WHI. WHIMS-MRI reported that while CEE+MPA and CEE-Alone were not associated with increased ischemic brain lesion volume relative to placebo; both CEE+MPA and CEE-Alone were associated with lower mean brain volumes in the hippocampus; frontal lobe; and total brain [47].

The evidence linking estrogen use with the prevention of Alzheimer's disease is still inconsistent. Some observational, case-control and cohort studies have shown reduced incidence of Alzheimer's disease in women using estrogen compared with nonusers. Not all studies have shown favorable results [18].

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## Principles of Treatment

### Patient Selection

Although there are alternative therapies for the treatment of vasomotor symptoms, none appear to be as effective in the short term as hormone

**Table 14.2** Hormonal therapy for vasomotor symptoms

Drug	Route	Dose
<i>17β-Estradiol micronized</i>	<i>Oral</i>	<b>0.5 mg</b>
<i>17β-Estradiol micronized</i>	<i>Oral</i>	<b>0.75 mg</b>
<i>17β-Estradiol + norethisterone acetate</i>	<i>Oral</i>	<b>2 mg + 1 mg</b>
<b>17β-Estradiol<sup>a</sup></b>	<b>Transdermal</b>	<b>25mcg, 50mcg, 100mcg</b>
<i>17β-Estradiol</i>	Implant	<b>25 mg</b>
<i>Nomegestrol acetate</i>	<i>Oral</i>	<b>5 mg</b>
<i>Medroxyprogesterone acetate</i>	<i>Oral</i>	<b>2.5 mg, 5 mg, 10 mg</b>
<i>17β-Estradiol + norethisterone acetate</i>	Transdermal	<b>50 mcg + 170 mcg</b>

<sup>a</sup>Initial therapy of choice, 50 mcg weekly [35, 36]

therapy, which is the gold standard treatment for most women with postmenopausal symptoms, except for those with a history of breast cancer, coronary heart disease, a previous thromboembolic event or CHD, or those at high risk for these complications. In the past, short-term therapy was defined as less than 5 years. This definition is somewhat arbitrary, since there is no consensus on the duration of treatment; nonetheless it seems reasonable, to use hormone therapy for a period of 3–5 years [18].

To date, postmenopausal HT, either using estrogen alone or in combination, should not be initiated for the prevention of cardiovascular diseases. Furthermore, postmenopausal HT is no longer considered a first-line option for the prevention and treatment of osteoporosis [18].

## Preparations

Both estrogen and progesterone present common features typical of the class of drug, but also with potentially different properties (Table 14.2). In the absence of clinical trials designed to compare different hormonal formulations it is necessary to generalize the results to all drugs belonging to this class. It is possible, however, to find differences within each family, such as potency, androgenicity, glucocorticoid effect, bioavailability, and route of administration.

Progesterone is recommended for all postmenopausal women with an indication for hormone therapy to prevent the risk of endometrial cancer in those women with an intact uterus [18].

## Dose and Route of Administration

Although it is not known whether lower doses of estrogen and progesterone have less effect on the cardiovascular system and the risk of breast cancer, it is recommended to use low hormone doses, when possible (e.g., 0.3–0.45 mg of oral conjugated estrogens, 0.5 mg of oral estradiol or 0.014–0.0375 mg of transdermal estradiol). In some studies, these doses have proved to be suitable for the treatment of symptoms. Many studies on the efficacy and safety of use of estrogen have used conjugated estrogen at a dose of 0.625 mg, considered to be the standard dose. Low-dosage preparations generally contain half this dose [48].

Low-dose estrogen formulations are also available in the form of gel, cream, ova pill and spray. The use of low hormonal doses sometimes requires a longer period of treatment to achieve maximum effectiveness in reducing vasomotor symptoms. Individualization of doses according to the woman's needs presents a good therapeutic strategy. Lower doses are associated with a lower incidence of side effects such as uterine bleeding and breast tenderness, and may have a more favorable risk-benefit ratio [18].

In a case–control study, the risk of CHD was not increased with use of low-dose transdermal estrogen (0.05 mg), but showed an increase with the use of oral and transdermal formulation with a higher dosage [49]. All routes of administration can effectively treat vasomotor symptoms. Non-oral routes of administration, including vaginal and intrauterine ones, and transdermal patches,

may offer both advantages and disadvantages compared to the oral route, but the long-term risk-benefit ratio has still not been demonstrated in clinical trials [18].

There are differences regarding the role of the hepatic first-pass effect, the hormone concentrations in the blood and the biological activity of preparations. With transdermal therapy there is no significant increase in triglycerides levels, C-reactive protein, hormone-binding globulin and the effect on arterial pressure. There is growing observational evidence that the transdermal route may be associated with a lower risk of deep vein thrombosis, CHD and myocardial infarction [18].

There are various dosage options of progesterone with no harm to the endometrium. The dose varies according to the progestin chosen and the estrogen system used, starting with the lowest effective doses, such as 1.5 mg of medroxyprogesterone acetate, 0.1 mg of norethindrone acetate, 0.5 mg of drospirenone, or 100 mg micronized progesterone. Oral progestogens, oral estrogen combinations, and combinations in the form of a patch have demonstrated endometrial protection and have been approved for use in postmenopausal hormone therapy. The use of progesterone—intrauterine or in the form of vaginal cream—has not yet been approved for postmenopausal women [18].

### **Duration of Treatment**

For postmenopausal women with moderate to severe vasomotor symptoms, and no contraindication for the use of estrogen, hormonal therapy is suggested as the treatment of choice. The lowest effective dose of estrogen should be used, with the shortest possible duration. Short-term therapy is considered as 2–3 years of use, and generally not more than 5 years. Only a minority of women unable to successfully discontinue treatment without the persistence of symptoms may be considered for a longer period of use, under close medical supervision [18].

### **Discontinuation of Treatment**

Many women do not have problems at the time of discontinuation of treatment. Observational studies suggest that 40–50 % of women discontinue hormone therapy 1 year after starting treatment, and 65–75 % stop in the second year, most often without medical follow-up. For other women the abrupt discontinuation of medication provokes the return of vasomotor symptoms and requires the resumption of treatment [18].

The North American Society of Menopause suggests that after a failed attempt to stop the therapy, prolonged use of postmenopausal hormone therapy may be reasonable for women who find that the benefits of symptom relief outweigh the risks. In this context, additional attempts are required at a later date for the discontinuation of postmenopausal hormone therapy [18].

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### **Complementary and Alternative Therapies**

#### **Non-hormonal Therapy for Vasomotor Symptoms**

$\alpha$ -Adrenergic agonists such as clonidine, have been used with variable success, although scientific data is contradictory [50]. A randomized clinical trial using oral clonidine showed no reduction in vasomotor symptoms. Normally, doses of 0.1 mg a day are required. Sometimes it can cause postural hypotension and have side effects in 50 % of users, including insomnia. Beta-blockers have been used for the control of anxiety and palpitation, but are not useful for hot flashes [51].

Serotonin selective reuptake inhibitors such as fluoxetine, paroxetine, and citalopram have been used in some studies. The most favorable finding indicates paroxetine at a dose of 10 mg per day, for higher doses were not associated with better symptom control. It may have adverse effects on the libido and should not be prescribed in patients with breast cancer using tamoxifen because it may modify the action of that drug [52].

**Table 14.3** Non-hormonal therapy for vasomotor symptoms [52]

Class	Drug	Dose
$\alpha$ -Adrenergic agonists	Clonidine	0.1 mg a day
Serotonin selective reuptake inhibitors	Fluoxetine	20 mg a day
Serotonin selective reuptake inhibitors	Paroxetine	10 mg a day
Serotonin selective reuptake inhibitors	Citalopram	20 mg a day
Selective noradrenaline reuptake inhibitors	Venlafaxine	75 mg a day
Structural analogue gamma aminobutyric acid	Gabapentin	900 mg a day

Selective noradrenaline reuptake inhibitors, such as venlafaxine, have been reported as effective in some small studies, especially in women with breast cancer unable to use hormone therapy. Usually venlafaxine is initiated at a dose of 37.5 mg and adjusted to a dose of 75 mg a day if necessary [52].

Gabapentin has also been used to relieve vasomotor symptoms in women with breast cancer. The dose used is usually 300 mg three times a day, but in order to reduce side effects, the dose may be gradually titrated, in other words, 300 mg per day for 2 weeks, 300 mg twice a day for two weeks, and finally, 300 mg three times a day after the first month (Table 14.3) [52].

### Other Hormone Therapies

In the USA dehydroepiandrosterone (DHEA) has been used to relieve vasomotor symptoms, but has not been widely used in other countries such as the UK. Some studies have shown beneficial effects on libido, bone metabolism, cognition, well-being, and vaginal lubrication. An uncontrolled pilot study showed a slight decrease in hot flashes using DHEA. Evidence on the use of natural progesterone cream is limited, with studies showing no symptom relief compared with placebo [53].

### Phytohormones

Phytoestrogens, nonsteroidal compounds that are naturally present in many plants, fruits, and vegetables, present both estrogenic and antiestrogen

activity. They are usually found in soybeans, lentils, flaxseed, grains, fruits, and vegetables. Data suggests that the lower risk of heart disease among Asian women compared with Western populations is due to the high consumption of soy products. This observation has led to an increasing interest in the potential use of phytoestrogens as an alternative to hormone therapy in postmenopausal women. In fact, an increasing percentage of women (including women with a history of breast cancer) use soy products in their diet to help control the symptoms of menopause. Moreover, many women believe that phytoestrogens, because they are “natural,” are safer than hormone therapy, although this has never been proven [54].

A review of the Cochrane Database of 30 randomized trials evaluated the efficacy, safety, and acceptability of foods and supplements, including all phytoestrogens. The reviewers concluded that there was no evidence that phytoestrogens help relieve menopausal symptoms [54].

### Botanicals

There is a wide range of natural products that have been used as a complementary therapy in menopause, without scientific evidence, such as St. John's wort, *Cimicifuga racemosa*, ginseng, dong quai, agnus castus, and *Ginkgo biloba* [55].

### Tibolone

Tibolone, a drug that has been widely used in Europe and other countries for almost 20 years, is a synthetic steroid whose metabolites have estrogenic, androgenic, and progestogenic properties. It reduces vasomotor symptoms when compared to placebo, and has a beneficial effect on bone mineral density. Limited data suggests that it may also have a modest effect on symptoms of sexual dysfunction. However, tibolone has been associated with an increased risk of stroke recurrence and possibly breast cancer, based on data from the LIFT and LIBERATE studies, respectively, and is therefore not recommended for routine use in the management of menopausal symptoms [56].



The LIFT trial, designed to examine the effect of tibolone on vertebral fractures in postmenopausal women, reported a reduction in the absolute risk of vertebral and non-vertebral fractures (8.6 and 6.9 per 1,000 person-years, respectively, relative hazards of 0.55, 95 % CI 0.41–0.74 and 0.74, 95 % CI 0.58–0.93, respectively). However, this trial was discontinued early, owing to an increased risk of stroke [57].

## Others

Vitamin E has been associated with decreased vasomotor symptoms in an isolated clinical trial [58]. Herbs of traditional Chinese medicine, reflexology, and magnetic devices have been studied, but have no beneficial effects [59]. Acupuncture has been studied as a potential therapy for hot flashes, but results so far are not promising [60].

## The Future

Although there is a real need to treat vasomotor symptoms and sleep disturbance in the menopausal transition, the long-term risks of hormone therapy preclude extended duration of use for the prevention of chronic disease. Although studies are currently under way to determine whether CHD risk will be impacted by the timing of initiation, the cancer risks are present at all ages, and some seem to persist after cessation of hormone therapy. The reduction in hip and vertebral fracture dissipates after stopping hormone therapy, whereas the long-term risk of breast cancer and possibly lung and ovarian cancers continues. Alternative therapies for menopausal symptoms that would not increase the risk of cancer are sorely needed. Because breast cancer seems significantly impacted by the use of progestin, ways to oppose estrogen's effect on the uterus without the use of a progestin are currently being developed. The combination of low doses of estrogen and a selective estrogen receptor modulator provides a new entity called a tissue-selective estrogen complex (TSEC). Early clinical trials suggests that some TSECs are effective in

reducing menopausal symptoms, increasing bone density, providing favorable lipid effects, while not increasing breast cancer risk and providing endometrial protection without a progestin. In particular, CEE and bazedoxifene are effective in reducing menopausal symptoms, have a favorable safety profile, improve bone density, and have few harmful side effects. Estrogen remains the most effective therapy for relief of vasomotor and other menopausal symptoms. The TSEC combination promises to be a significant improvement in the relief of vasomotor symptoms with potentially lower risks than traditional HT [35].

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## Pathophysiology

The male reproductive tract is in constant interaction with the hypothalamic–pituitary–testes, to produce and secrete androgenic hormones (HA) and produce, maintain, and transport sperm and seminal fluid, thus enabling the male fecundity. The HA are critical for embryonic differentiation of internal and external male genitalia, development and maintenance of secondary sexual characteristics, and androgenic effects of extra-gonadal [1].

During embryonic development, primordial gonads during the first weeks of pregnancy will suffer a cascade of events that culminate in sexual differentiation. The gonads undifferentiated germ cells do not have that subsequently will differentiate into Sertoli cells and interstitial cells differentiate into Leydig cells constituting the endocrine testicular tissue. In the presence of sex chromosomes XY, from the seventh week of pregnancy, start will be the activity of the gene SRY (sex-determining region on the Y chromosome), located on the short arm of the Y chromosome, which encodes a protein that, together with other factors encoded by other chromosomes

(autosomal or X chromosome), will act in embryonic differentiation from primordial gonad. Sertoli cells secrete the anti-mullerian hormone that promotes regression of Mullerian ducts. After about 8 weeks of gestation, the Leydig cells will already have the capacity to produce steroids and, together with the stimulation of human chorionic gonadotropin (hCG) produced by the placenta will secrete testosterone, beginning the process of stabilizing Wolff ducts and with that the differentiation of the internal sexual organs. The differentiation of testosterone into dihydrotestosterone (DHT) by the enzyme  $5\alpha$ -reductase will cause DHT stimulates the differentiation of the external genitalia [2, 3].

The synthesis of testosterone occurs in Leydig cells (compartment interstitial) in response to stimulation of luteinizing hormone (LH). The spermatogenesis in the seminiferous tubules is dependent on the action of follicle stimulating hormone (FSH) in Sertoli cells (germ cells) and by the action of testosterone. Approximately 95 % of the testes match compartment germ cell, which explains the enormous daily production of sperm. The gonadotropins (LH and FSH) are produced in the pituitary in its anterior portion (gonadotrophes) through stimulation of GnRH produced in the hypothalamus, which is transported through the pituitary portal system [4]. Testosterone is the principal androgen plasma in men, is synthesized predominantly in testes, and small quantities, adrenal glands. The circulating testosterone (total testosterone) represents the set of existing forms, being the absolute value of

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testosterone, 2 % in its free form, coupled to 44 % of androgen binding protein (SHBG, steroid hormone binding globulin) and 54 % bound to albumin [3].

Testosterone is the most important testicular androgen in men. Low serum testosterone levels are associated with cardiovascular morbidity, metabolic syndrome, type 2 diabetes mellitus, atherosclerosis, osteoporosis, sarcopenia, and mortality. There is increasing evidence that serum testosterone is a major biomarker status of men's health in general. Studies in twins indicate that an individual there is a strong heritability of serum testosterone. Research based on genome has sought to evaluate the effects of genetic variants on serum concentrations of testosterone. Analysis 14,429 men showed that genetic variants in SHBG and on their locus on the X chromosome are associated with a wide variation in serum testosterone concentrations and an increased risk of their low levels. A genetic variant that affects the affinity of testosterone to SHBG, interfering directly in its free fraction, could influence the mathematical calculations that estimate their serum. Thus, in the future it may be necessary to evaluate the affinity of testosterone to SHBG and this is taken into account in the measurements of serum levels, as well as analysis of genetic polymorphisms closely related to these variables [5].

The testicular disorders can be classified into disorders of production and/or action of sex steroids, disorders of spermatogenesis and testicular neoplasms. The male hypogonadism and gynecomastia are the most prevalent disorders in the production of sex steroids in men. Defects in androgen action include mutations in different receptors (androgen, estrogen- $\alpha$ ) and enzymes (5- $\alpha$  reductase, aromatase). The defects of spermatogenesis will characterize infertility or sub-fertility [1].

Male hypogonadism is a syndrome associated with disturbances of the production or action of testosterone and/or disorders in spermatogenesis. Testosterone deficiency can result from abnormalities in testicular function, such as disorders in testosterone production and/or spermatogenesis disorders (primary hypogonadism), the regulation of the hypothalamic pituitary or testicular function (secondary hypogonadism), or disorder action of in androgen target tissues (androgen

insensitivity). Testosterone deficiency may occur as a result of Leydig cell dysfunction in primary hypogonadism by insufficient secretion of GnRH and/or LH at secondary hypogonadism (pituitary and hypothalamic) [6].

The primary gonadal failure may be due to congenital and acquired disorders. Already a secondary gonadal failure may be due to functional or organic abnormalities (congenital and acquired) [Table 15.1]. The primary testicular failure is characterized by low levels of testosterone and/or disorders of spermatogenesis associated with high concentrations of LH and FSH (hypergonadotropic hypogonadism). Secondary testicular failure is associated with low testosterone levels and inappropriately normal or low concentrations of LH and FSH (hypogonadotropic hypogonadism).

Secondary hypogonadism is usually associated with similar decreases in sperm and testosterone production. This occurs because the reduction in LH secretion promotes a reduction of testosterone production in the testes and, consequently, of intratesticular testosterone (primary hormonal stimulus for the production of sperm). In primary hypogonadism may be a decrease in spermatogenesis in major damage in the cells of the seminiferous tubules (Sertoli cells) than in Leydig cells. When this occurs, the subjects may present LH and testosterone levels normal, even with a number of ejaculated sperm very low or near zero. In these cases, FSH levels will meet high.

In cases of secondary hypogonadism also there is less susceptibility to the occurrence of gynecomastia, probably due to normal or low levels of FSH and LH which do not stimulate aromatase testicular, not increasing the conversion of testosterone to estradiol.

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## **Causes of Hypogonadism**

### **Primary Hypogonadism (Hypergonadotropic)**

#### **Congenital Causes**

##### **Klinefelter Syndrome (KS)**

The Klinefelter syndrome is the most common sex chromosomal disorder in men, affecting one

**Table 15.1** Causes of Hypogonadism*Primary hypogonadism**Congenital*

1. Chromosomal disorders
  - (a) *Klinefelter syndrome and related syndromes (such as Male 46 XX)*
  - (b) *Defects enzyme in the biosynthesis of testosterone*
  - (c) *Myotonic dystrophy*
2. Developmental disorders
  - (a) *Exposure to endocrine disruptors prenatal*
  - (b) *Cryptorchidism*
  - (c) *Anorchia due to bilateral torsion testes syndrome or missing*
  - (d) *Noonan Syndrome*

*Acquired*

1. Orchitis
2. Mumps and other viruses
3. Infiltrative diseases (such as amyloidosis, hemochromatosis)
4. Acquired immunodeficiency syndrome (AIDS)
5. Granulomatous diseases (such as leprosy and tuberculosis)
6. Irradiation
7. Surgical lesions
8. Trauma and testicular torsion of the testicle
9. Varicocele
10. Autoimmune testicular failure
  - (a) *Isolate*
  - (b) *Associate (as Hashimoto's thyroiditis, diabetes mellitus type 1)*
11. Drugs
  - (a) *Anti-androgenic steroids (as flutamide, cimetidine, cyproterone, spironolactone, ketoconazole)*
  - (b) *Cytotoxic*
12. Endocrine disrupting (such as insecticides, heavy metals, gossypol, environmental estrogens)

*Androgen resistance syndrome*

1. Testicular feminization syndrome (Morris syndrome)
2. Reifenstein syndrome

*Secondary hypogonadism**Congenital*

1. Multiple pituitary hormone deficiency
2. Pituitary aplasia or hypoplasia
3. Defects in the secretion or action of GnRH
  - (a) *Mutation Kalig-1*
  - (b) *Mutation in GnRH receptor*
4. Defects in the action or secretion of gonadotropins
  - (a) *Inactivating mutations of the LH- $\beta$  gene*
  - (b) *Inactivating mutations of the LH receptor gene*
  - (c) *Inactivating mutations of the FSH- $\beta$  gene*
  - (d) *Mutation in DAX-1 and SF*
5. GnRH deficiency
  - (a) *Isolated (Idiopathic hypogonadotropic or hypogonadism Isolated)*
  - (b) *With anosmia (Kallmann syndrome)*
  - (c) *Associated with other abnormalities (Prader-Willi syndrome, Laurence-Moon and Bardet-Biedl syndrome, CHARGE syndrome, Rud syndrome, multiple lentigenes, basal encephalocele, cerebellar ataxia)*
  - (d) *Partial deficiency of GnRH (Fertile eunuch syndrome)*

(continued)

**Table 15.1** (continued)

<i>Acquired</i>	
1.	Traumatic Brain Injury
2.	Post-Radiation CNS (central nervous system), post-surgery, pituitary infarction, carotid aneurysm
3.	Neoplasms
	(a) <i>Pituitary Adenomas: prolactinomas, nonfunctioning adenomas, others adenomas</i>
	(b) <i>Craniopharyngioma, germinomas, gliomas, lymphomas</i>
4.	Autoimmune hypophysitis
5.	Functional disorders: anorexia nervosa, dysfunction secondary to stress or other systemic diseases
6.	Infiltrative disease: sarcoidosis, histiocytosis cells Langhans, hemochromatosis
7.	Infectious diseases: tuberculosis, histoplasmosis, abscesses
8.	Drugs
9.	Endocrine disrupting
<i>Combined hypogonadism</i>	
1.	Aging
2.	Alcoholism
3.	Hemochromatosis
4.	Sickle cell anemia
5.	Congenital adrenal hypoplasia (mutation of DAX-1)
6.	Endocrine disrupting

in every 660 children born alive [7]. It was first described in 1942. KS has a genetic background, with characteristics involving various specialties as embryology, pediatrics, endocrinology, cardiology, psychology, psychiatry, urology, and epidemiology.

Genetic inheritance is the extra X chromosome, which can be inherited from either parent. Most genes undergo additional X inactivation, but some may escape and serve as a genetic cause of the syndrome. Of these genes, the one that has been clearly shown to influence the phenotype of KS was short-stature home box-containing gene on chromosome X (SHOX) located pseudoautosomal region 1 in Xp. The haploinsufficiency of SHOX gene has been implicated in growth retardation and bone abnormalities in Turner syndrome and Leri-Weill of discondrosteose and is also implicated in the growth accelerated slightly in KS [8]. The karyotype more frequent in men with Klinefelter syndrome is 47, XXY (93 %) but were reported karyotypes 46, XY/47, XXY; 48, XXXY; 48, XXYY; and 49, XXXXY [7].

KS is commonly under diagnosed or is diagnosed late. Most men with KS live without a diagnosis. Boys with KS are likely to receive a diagnosis during evaluation for developmental

delay and behavioral issues. Men with KS usually call attention during evaluation for infertility or hypogonadism. Only 25 % of cases are diagnosed and the average age of diagnosis is 30 years. A recent Australian study found a prevalence of 223 cases per 100,000 live births boys [9], proposing an increase in the prevalence observed in several previous studies [10] and suggesting that she should differ between populations.

KS is associated with an increased morbidity resulting in loss of life, an increase in mortality due to various diseases. Large epidemiological studies in KS were performed in two main cohorts: the British study [11] and Danish [12]. Together these studies show that the expected lifetime was reduced by 1.5–2 years, with increased mortality various diseases including diabetes, pulmonary disease, epilepsy, cerebrovascular disease, and vascular insufficiency of the intestine. In both studies, mortality among men with KS was significantly greater (hazard ratio: 1.9) and remained so after adjustment for social cohesion and education level (hazard ratio: 1.5), indicating that socioeconomic parameters can explain some but not all excess mortality in KS.

The main findings of KS are small testes, hypergonadotropic hypogonadism and cognitive

**Table 15.2** Abnormalities associated with Klinefelter syndrome

Feature	Frequency (%)
Infertility (adults)	91–99
Small testes (both testes <6 mL)	>95
Increased gonadotropin	>95
Azoospermia (adults)	>95
Commitment to learning (children)	>75
Decreased testosterone	63–85
Decreased facial hair (adults)	60–80
Decreased pubic hair (adults)	30–60
Gynecomastia (teens/adults)	38–75
Delay in speech development (children)	40
Increase height (prepubertal/adults)	30
Adiposity (adults)	50
Metabolic syndrome (adults)	46
Osteopenia (adults)	5–40
Diabetes mellitus type 2	10–39
Cryptorchidism	27–37
Reduced penis size (children)	10–25
Psychiatric disorders (children)	25
Congenital malformations, ogival palate, inguinal hernia	18
Osteoporosis (adults)	10
Mitral valve prolapse (adults)	0–55
Breast cancer (adults)	Increased risk (50 times)
Mediastinum cancer (children)	Increased risk (500 times)
Fractures	Increased risk (2–40 times)

impairment. Other abnormalities are associated with KS and its frequency is varied (Table 15.2) [7].

Azoospermia is found in the vast majority of men with KS who have the karyotype 47, XXY. The mechanism by which an extra X chromosome causes infertile patients is not well known. Men with germ cell mosaics can present in their testicles, especially at a younger age. The testicular histology in men with KS shows hyalinization of seminiferous tubules and absence of spermatogenesis. Patients with mosaics may show normal-sized testes and spermatogenesis in puberty. However, the progressive degeneration and hyalinization of seminiferous tubules occur soon after puberty. Therapeutic advances with the use of ICSI (Intracytoplasmic Sperm Injection) allow

men 47, XXY azoospermic can achieve biological fatherhood [13].

The behavioral phenotype of KS is characterized by dysfunction of language, executive and psychomotor impairment and socio-emotional. Boys with KS often need speech therapy treatment, and many suffer from learning difficulties and may benefit from special education. The prevalence of schizophrenia, attention deficit hyperactivity disorder, autism spectrum disorders, and problems with mood regulation is increased. Neuroimaging studies of children and adults with KS show increases in the volume of gray matter regions of sensorimotor and parietoccipital, as well as significant reductions in the amygdale, hippocampus, insular, temporal and inferior frontal volumes of gray matter [14].

Hypogonadism in KS may lead to changes in body composition and risk of developing metabolic syndrome and diabetes type 2. Medical treatment is mainly testosterone replacement therapy to relieve acute and long-term hypogonadism, as well as treatment or prevention of comorbidities.

### Other Chromosomal Abnormalities

Other chromosomal abnormalities that result in testicular hypo function were reported, including rare diseases 46, XY/XO and 47, XYY. The karyotype 46, XY/XO leads to a syndrome characterized by short-stature and other typical features of Turner syndrome. The gonad digenesis varies from the normal testes. The risk of gonadoblastoma is about 20 % if digenesis. Gonadectomy should therefore be conducted in these patients [15, 16]. The karyotype 47, XYY was initially associated with hypogonadism, but other reports have not confirmed this relationship further. Micro deletions specific regions of the long arm of chromosome Y can be detected in approximately 20 % of men with severe oligospermia or azoospermia. Some of these men have no other testicular lesions, but others have cryptorchidism [17].

Myotonic dystrophy, an autosomal dominant disease, leads to muscle atrophy and is accompanied by hypogonadism that is usually not recognized



until adulthood. Small testes and decreased production of sperm are more common than reduction of serum testosterone levels [18, 19].

### Disorders of Androgen Synthesis

Mutations in genes encoding the enzymes necessary for the biosynthesis of testosterone may result in a decrease in their serum. The rare mutations found are enzyme cleavage of the side chain of cholesterol, 3 $\beta$ -hydroxysteroid dehydrogenase, and 17 $\alpha$ -hydroxylase (present in the adrenals and testes) and 17 $\beta$ -hydroxysteroid dehydrogenase (present only in the testes). Depending on the degree of mutation meet differing degrees of fetal virilization [20].

### Mutation in FSH and LH Genes

Changes in LH and FSH receptors are rare causes of primary hypogonadism. The mutation in the FSH receptor induces sperm count variable which tend to be generally low and concentrations of inhibin B and FSH levels. Mutations in LH receptor results in hypoplasia and Leydig cell testosterone deficiency in the first trimester in utero, resulting in different degrees of DDS (disorder of sexual development) [21–23].

### Cryptorchidism

Cryptorchidism refers to topics that are not testicles in the scrotum. The main sites are found: inguinal canal and abdominal cavity. It is necessary to differentiate between the possible cryptorchid testes and testicles shrink, that manipulation, return to the scrotum normally. Cryptorchidism can affect one or both testes. If only one is affected testes, sperm count is subnormal in 30 % of cases (and the concentration of FSH is slightly raised), suggesting that even in the presence of a testes topic, this may present different degrees of testicular dysfunction. If both testes are cryptorchid, sperm count is usually severely impaired and serum testosterone may also be reduced. The gonadoblastoma risk also increases if the testicle is not in its normal position [24, 25].

### Congenital Anorchia

Congenital anorchia occurs in disorders (after 20 weeks of gestation) that lead to testes regression.

The male sex differentiation at birth is normal, but the testes are absent and hypogonadism in general is important [26]. The diagnosis is confirmed after anorchia full search of imaging studies (both in scrotal, and in the abdominal cavity) and, if necessary, laparotomy. There are case reports that testosterone treatment in adult men with congenital anorchia and micropenis and can lead to increased penile.

### Acquired Causes

#### Varicocele

Damage to the seminiferous tubules due to varicosity of the venous plexus within the scrotum has been considered a possible cause of male infertility. Current data are conflicting about the real benefit of varicocele correction in relation to fertility [27].

#### Orchitis

Several infections may be associated with testicular damage. The most common cause is mumps and orchitis is a frequent manifestation occurs when adulthood. The incidence has decreased due to the vaccination of the population. The involvement of testicular mumps causes increased painful testicles, followed by atrophy. The seminiferous tubules are often severely affected, often resulting in infertility, especially when both testicles are involved. The Leydig cells can also be damaged, resulting in decreased production of testosterone.

### Chronic Diseases

Gonadal dysfunction is a common finding in men with chronic kidney disease (CKD) and end-stage disease. Testosterone deficiency generally accompanied by elevated serum gonadotropin is present in 26–66 % of men with varying degrees of renal impairment. Uremia-associated hypogonadism is multifactorial in origin, and rarely improves with the onset of dialysis, although usually normalizes after renal transplantation. While there are encouraging data suggesting benefits of testosterone replacement therapy for CKD patients, more studies are needed regarding the safety and efficacy of therapeutic [28].

**Table 15.3** Estimated risk of gonadal dysfunction with cytotoxic agents

High risk	Medium risk	Low risk
Cyclophosphamide	Cisplatin	Vincristine
Ifosfamide	Carboplatin	Methotrexate
Chlormethine	Doxorubicin	Dactinomycin
Busulfan	BEP	Bleomycin
Melphalan	ABVD	Mercaptopurine
Procarbazine		Vinblastine
Chlorambucil		
MOPP		

*ABVD* adriamycin, bleomycin, vinblastine, and dacarbazine; *BEP* bleomycin, etoposide, and cisplatin; *MOPP* nitrogen mustard, oncovina (vincristine), procarbazine, and prednisone

The gonadal function requires a normal liver function. It is well known that the clinical symptoms of hypogonadism are common in patients with liver cirrhosis. The pathogenesis of hypogonadism in cirrhotic patients is complex and not well explained. It involves both a gonadal dysfunction as a disturbance centrally [29]. Hypogonadism is a potential complication of hemochromatosis, usually seen in patients with severe iron overload and liver cirrhosis [30].

Other infiltrative or granulomatous disease may promote primary gonadal failure, varying clinics demonstrations and testicular dysfunction according to the degree of involvement of the underlying disease. Examples are tuberculosis, leprosy, among others.

### HIV Infection

Men who have HIV may be hypogonadism varying degrees. The premature decline of serum testosterone is common (16 %) among young men and middle-aged HIV-infected and is associated with inappropriately low or normal LH and accumulation of visceral adipose tissue. Testosterone deficiency occurs in young people infected with HIV and may be regarded as a process of accelerated or premature aging. The role of HIV and/or treatment of HIV infection have yet to be elucidated [31]. The frequency of hypogonadism and its severity appear to have decreased since the introduction of antiretroviral therapy.

### Irradiation

The direct radiation to the testes, as the treatment for leukemia, can damage them. Even when

radiation is indirect, damage may occur in the seminiferous tubules. The degree of damage is proportional to the amount of radiation exposure. Radioactive iodine may cause a decrease in sperm count when the doses administered are high for treatment of differentiated thyroid carcinoma.

### Gonadal Toxicity of Cancer Chemotherapy

The number of surviving young men cancer has increased dramatically over the past 20 years as a result of early detection and better treatment protocols for cancer. Over 75 % of cancer patients diagnosed in youth are long-term survivors.

The gonadal dysfunction has emerged as an important long-term complication of cancer chemotherapy, especially in young patients with hematological malignancies and testicular. Infertility can be a significant issue for many cancer survivors. The male hypogonadism after chemotherapy may contribute to fatigue, sexual dysfunction, irritability, loss of lean mass, and osteopenia. Quality of life and recovery from cancer treatment is worsened by this clinical.

Cytotoxic chemotherapy might cause injury gonadal, and the nature and extent of the damage depends on the drug, the dose received and age of the patient. Many drugs are toxic (Table 15.3) including procarbazine, cisplatin, and alkylating drugs such as cyclophosphamide, melphalan, chlorambucil. However, all chemotherapeutic drugs can cause damage to gonadal function [32]. The relative contribution of each individual drug can be difficult to determine because most treatments are conducted with multiple drug regimens [33].

### Trauma and Torsion of Testes

Any trauma in the testes may be sufficient to damage both the seminiferous tubules as Leydig cells. The testicular torsion is one of the most common reasons for the loss of a testicle before puberty. The torsion of testes is a twist in the spermatic cord, which results in severe loss of blood to the testes. The loss of the testes can occur due to lack of blood if the twist is not reverted spontaneously or surgically corrected within a few hours. The degree of damage depends on the length of twist. Twist that lasts more than 8 h can promote enough damage to decrease the sperm count. Even when the twist involves only one testicle, both testicles may be damaged, it is not clear how this can occur [34–36].

### Medications

Ketoconazole directly inhibits the biosynthesis of testosterone, thereby causing there is deficiency in the production [37]. Chronic use of glucocorticoids can also decrease testosterone levels in about one-third of individuals. The mechanism is not clear, but the inhibition can occur in both testes and pituitary gland [38, 39].

### Autoimmune Testicular Failure

It may occur in isolation or as a manifestation of polyglandular autoimmune syndrome. Should be considered in all patients with other concomitant autoimmune diseases [40].

## Secondary Hypogonadism (Hypogonadotropic)

### Congenital Causes

The etiology of congenital gonadotropin dysfunction is rare. Clinical findings vary among individuals mainly due to the time of onset of dysfunction of gonadotropins. Sexual differentiation is normal because testosterone secretion by Leydig cells in fetal first trimester of pregnancy is dependent stimulation of placental hCG. The penile development occurs primarily during the third trimester of pregnancy, and is often subnormal

because testicular testosterone secretion at this stage is dependent on LH secretion fetal which is also subnormal. This results in many cases in micropenis. The linear growth in childhood is normal, deficits occurring only when associated with deficiency in the production of growth hormone or thyroid hormone. Most diagnoses are made during puberty. This can initiate and submit slowing in its evolution, becoming in many cases incomplete. Some patients, depending on the degree of gonadotropin deficiency, delayed puberty may present or absent [41].

### Isolated Hypogonadotropic Hypogonadism

It is characterized by isolated deficiency of gonadotropins, without changes in smell and due to deficient secretion of GnRH, GnRH receptor mutation or mutations of  $\beta$  fractions of LH or FSH. Several genetic mutations may be involved in the production process, hormonal secretion or action (Table 15.4). Many cases remain of unknown etiology [42, 43].

### Kallmann Syndrome

Kallmann syndrome is characterized by hypogonadotropic hypogonadism and another congenital abnormality not gonadal, including anosmia or hyposmia, red-green daltonism, midline facial defects, abnormalities of the urogenital tract, synkinesis (mirror movements), and sensorineural hearing loss. Hypogonadism is due to deficient secretion of GnRH due to defects in the migration of GnRH-secreting neurons that have the same embryological origin those olfactory neurons. Most cases are sporadic, but there may be a familial transmission (X-linked inheritance is autosomal dominant or recessive). Studies have shown mutations in genes encoding several adhesion molecules on the cell surface, receptors or necessary for the migration of neurons, such as fibroblast growth factor receptor 1 (also called KAL1) prokineticin-2 (PROK2) and its receptor (PROKR-2). These mutations together represent less than half of the cases described [22, 23, 42, 44].

**Table 15.4** Genes involved in the etiology of hypogonadotropic hypogonadism [22, 23, 43, 44, 47]

Gene	Product	Function	Clinical
CHD7	Protein linker of cromodomínio-type DNA helicase-7	Development of the neural crest, protein bound to DNA	CHARGE syndrome—semicircular canal aplasia, hypoplasia of the olfactory bulb, GH deficiency, hypothyroidism, congenital malformations that include hypogonadotropic hypogonadism (with micropenis and/or cryptorchidism)
DAX1/ NR0B1A	Gene 1 of sex reversal	Development of adrenal, secretion of gonadotropins control	Adrenal hypoplasia congenital X-linked (primary adrenal insufficiency that is expressed in the early stages of life)
FGF8	Fibroblast growth factor type 8	FGFR1 Binder/migration of GnRH neurons	Kallmann syndrome
FGFR1	Receptor type 1 fibroblast growth factor (FGF receptor 1)	Migration of GnRH neurons	Kallmann syndrome
FSH $\beta$	B subunit of FSH	Binder receptor FSH	Isolated FSH deficiency (azoospermia, small testes in soft and undetectable serum FSH)
GnRH1	Pre hormone GnRH	GnRH synthesis and cell signaling	Isolated hypogonadotropic hypogonadism
GnRHR	GnRH receptor	Synthesis of LH and FSH	Isolated hypogonadotropic hypogonadism, LH-isolated deficiency (partial mutations)
GPR54/ Kiss1R	Receptor 1 of Kisspeptin	Stimulation of secretion of GnRH	Isolated hypogonadotropic hypogonadism with attenuated LH response to exogenous GnRH stimulation
HESX-1	Homeobox protein ANS	Marking the previous visceral endoderm embryo	Syndrome of septo-optic dysplasia (optic nerve hypoplasia, radiological changes of online medical and hypoplastic anterior pituitary (hypopituitarism with neuro ectopic posterior pituitary) and Pickardt-Fahlbush syndrome
HS6ST1	6-O-sulfotransferase heparin sulfate	Catalyzes transfer of the sulfate at position-6 in the biogenesis of heparin sulfate	Hypogonadotropic hypogonadism
KAL1	Anosmin-1	Cell adhesion glycoprotein (expressed in embryonic development in olfactory bulb, cerebellum, spinal cord, kidney, and retina), migration of GnRH neurons	Kallmann Syndrome
LEP	Leptin	Hormone regulating food intake, energy expenditure, and hypothalamic reproductive function	Homozygous mutation in the leptin exhibit morbid obesity and hypogonadism (apparently of hypothalamic origin)
LEPR	Leptin Receptor	Membrane receptor	Morbid obesity and hypogonadism (apparently of hypothalamic origin)
LHX3		Transcription factor required for the development of pituitary	Hypopituitarism (corticotrophic preserving function) associated with limitation of neck rotation (rigid cervical spine), elevated and anteverted shoulders
LH $\beta$	B subunit of LH	Binder receptor LH	Isolated FSH deficiency (fertile eunuch syndrome—deficient production of testosterone associated with varying degrees of spermatogenesis)
NELF	Factor nasal embryonic LHRH	Neuronal migration	Hypogonadotropic hypogonadism
PROK2	Type 2 prokineticin	Migration of GnRH neurons	Kallmann Syndrome
PROKR2	Receptor Type 2 prokineticin	Migration of GnRH neurons	Kallmann Syndrome
TAC3	Neurokinin B	Binder TACR3, Stimulates GnRH secretion	Hypogonadotropic hypogonadism
TAC3R	Neurokinin B receptor	Stimulates the secretion of GnRH	Hypogonadotropic hypogonadism
WDR11	Protein WD	Interaction with transcription factor EMX1/GnRH neuronal migration	Hypogonadotropic hypogonadism

### Laurence-Moon and Bardet-Biedl Syndrome

Etiologies of hypogonadism associated with retinitis pigmentosa and developmental delay. In Laurence-Moon syndrome is associated with spastic paraplegia and Bardet-Biedl associated with post axial polydactyly, renal dysplasia, and early-onset obesity [45, 46].

### Deficiencies of Transcription Factors

Some individuals have involvement of other hormonal axes in association with gonadotropin deficiency. Mutations in PROP-1 gene is the most common genetic cause of sporadic cases of hypopituitarism and family [22, 23].

### Acquired Causes

Hypogonadotropic hypogonadism can be caused by any disease that interferes with the hypothalamic–pituitary axis. The mechanisms that may be involved (one or more) are hypothalamic disorders (impair the GnRH secretion), disorders of the pituitary stalk (interfere with the passage of GnRH into the pituitary gland) and pituitary disorders (directly decrease the secretion of LH and FSH).

### Disorders of Gonadotropin Secretion

#### Hyperprolactinemia

Hyperprolactinemia due to any cause can suppress gonadotropin secretion and thus testicular function [48]. Hypogonadism is reversible with normalization of the prolactin.

#### Drugs

##### – *Sexual Steroids:*

The use of androgen, estrogen, or progesterone may alter the secretion of gonadotropins. The recreational use of male sex hormones can interfere aiming anabolism in the secretion of gonadotropins during the period that is being used and, after several months of drug withdrawal when high doses are used. Recent data show that abuse of androgens can lead, in addition to hypogonadism, increased cardiovascular morbidity and mortality [49]. Estrogens and progestins used as appetite stimulants can promote a secondary hypogonadism in some individuals.

##### – *Glucocorticoids:*

Chronic treatment with glucocorticoids can lead to hypogonadism. Prolonged use in various diseases in current medical settings, and the indiscriminate use of steroids, showed the effect of medication on the pulsatility of gonadotropins and consequently on gonadal function [38].

##### – *Opiates:*

When administered chronically, especially when continuing to control chronic pain, often cause pronounced hypogonadism [50, 51]. Opioids, endogenous and exogenous, modulate gonadal function, acting mainly on opioid receptors in the hypothalamus, decreasing the secretion or causing loss of pulsatility normal gonadotropin releasing hormone (GnRH). Opioids may also have direct effects on the pituitary gland and testes [52].

##### – *GnRH Analogs:*

The prolonged administration of GnRH analogues leads to a decrease in the secretion of LH and hence the secretion of testosterone. Currently, drugs as triptorelin and histrelin are much used in the adjuvant treatment of prostate cancer [53].

#### Chronic Diseases

Several systemic and chronic diseases, including cirrhosis, chronic kidney failure, chronic lung disease, and AIDS, cause hypogonadism by a combination of primary and secondary effects [54].

#### Critical Conditions

Any serious illness, surgery, myocardial infarction can cause hypogonadism. Decreased levels of LH is found in critically ill patients, suggesting an involvement in the pituitary gonadal function [55, 56].

#### Anorexia Nervosa

Although less common in adolescent males, anorexia in boys may also be associated with secondary hypogonadism characterized by functional hypothalamic changes, interfering with the proper secretion of GnRH [57].

#### Diabetes Mellitus (DM)

Males DM2 patients have a higher prevalence of low serum concentrations of testosterone than

men without diabetes. The pathogenesis of this disorder is still uncertain, but it is known that there is a decrease in both total testosterone as its free fraction. The DM2 patients have other signs and symptoms of metabolic syndrome, which may contribute to further enhance the hormonal deficit [58–62].

### Obesity

The European Male Aging Study demonstrated that men who are overweight (BMI 25–29 kg/m<sup>2</sup>) and those who are obese (BMI ≥ 30 kg/m<sup>2</sup>) tend to have lower serum concentrations of the hormone binding globulin (SHBG) and, therefore, lower serum total testosterone. Inasmuch as the concentration of total serum testosterone to SHBG is due to low concentration of free testosterone is normal. However, men who are obese may also have low levels of free testosterone. At all ages, total testosterone and SHBG concentrations were lower in overweight men than in men of normal weight and even lower in obese men. Free testosterone was similar in men with normal weight and overweight, but lower in obese men. Serum concentrations of LH did not increase in patients with BMI above the normal range, demonstrating a disorder in the central gonadal axis [61–63].

## Disorders of Direct Gonadotroph

### Benign Tumors and Cysts

Pituitary adenomas and sellar cyst can cause decreased cell function by gonadotropic local mass effect, decreasing the release of LH and FSH.

### Neoplasms

Malignant tumors of the central nervous system metastases or other malignancies can affect the functioning of the gonadal axis by interfering with the production of gonadotropins. Meningiomas are among the most common primary tumors and metastatic lesions of lung cancer and prostate cancer.

### Infiltrative Diseases

Sarcoidosis and Langerhans cell histiocytosis (eosinophilic granuloma) can cause hypothalamic

hypogonadism. The iron deposition in patients with hemochromatosis directly on the pituitary can induce secondary hypogonadism.

### Infections

Tuberculosis meningitis and other causes of CNS infections may promote central hypogonadism. In most cases there is a concomitant involvement of other pituitary axis.

### Traumatic Brain Injury (TBI)

The ECA has been described in recent years as an important cause of hypopituitarism, including GH deficiency and male hypogonadism. Injuries slowdown, leading concusses brain trauma and skull base can pull the pituitary stalk and sectional portal circulation. However, most of the dysfunctions of the hypothalamic–pituitary are still poorly understood, demonstrating a high rate of hypogonadism during acute trauma with subsequent recovery of gonadal function in a group of patients remaining in permanent hypogonadism 10–15 % of individuals 1 year after the event. The time of recovery of gonadal function and the reason for the fall of gonadotropins in acute moment is still a matter of discussion and research [64].

### Endocrine Disruptors and Gonadotropic Axis

Endocrine disruptors compounds (EDCs) are exogenous compounds that have the potential to interfere in regulating the endocrine system and therefore may predispose to disease in man and animals [65]. The EDCs can be naturally derived from plants (phytoestrogens) in animals and man. Currently, artificial chemical compounds are of major concern worldwide. EDCs can interfere with the production, secretion, metabolism, transport or in the peripheral action of endogenous hormones through its binding to hormone receptors.

Evidence of changes in human male reproductive tract associated with EDCs is still limited. Humans are exposed to hundreds or thousands of environmental chemicals and a major limitation of epidemiological studies is that generally measure human exposure to a single EDC [65, 66].

**Table 15.5** Association of EDCs and possible diseases of the human male reproductive system

Stage of development	Disease/associated amendment
Fetal	Cryptorchidism, hypospadias, testes dysgenesis syndrome
Prepubertal	Precocious pubarche
Pubertal	Testes atrophy, precocious puberty, delayed puberty
Adult	Infertility, testes cancer, and enlarged prostate

The male sex differentiation is androgen-dependent. Thus, various diseases can be observed in males due to exposure to EDCs. Postnatal exposures also have impact on development and maintenance gonadal males (Table 15.5).

#### Quality of Semen

The decline in semen quality lifelong learning has been followed in several countries. Some studies suggest that semen quality decreases before 50 years of age, while others do not observe this decline [66].

Despite the importance and relevance of exposure to EDCs, especially polychlorinated biphenyls (PCBs), pesticides, and phthalates, the epidemiological evidence on the relationship with semen quality in adults is still limited, mainly because many of the data were obtained transversely.

#### Testes Dysgenesis Syndrome

Testes dysgenesis syndrome (TDS) is the association between cryptorchidism, hypospadias, and testicular cancer oligozoospermia resulting from altered testicular development. This association may mean that several elements acted at different times throughout the life of an individual, and may be due to exposure to a particular EDC or their mixture. However, epidemiological data concerning EDCs with this syndrome in humans are still indirect [67].

The decreased anogenital distance, a marker of prenatal androgen activity was observed in rats exposed to phthalates in the prenatal period and later identified in an epidemiological study with newborn human males [68].

#### Male Urogenital Tract Malformation

The association of exposure of father and/or mother or a community to pesticides with hypospadias or cryptorchidism presence in newborns is suggestive of the involvement of EDCs. Epidemiological data supporting this link are those from individuals living in agricultural areas and/or that directly assessed the exposure of parents to organochlorine pesticides-not [69].

#### Testicular Germ Cell Cancer

The frequency of testicular germ cell tumors (TGCT), which comprises more than 95 % of all testicular cancers, increased significantly during the past four decades, well beyond the expected population growth. To date, the evidence on the relationship between EDCs and risk of TGCTs are limited. Interestingly, in a case-control study, no association was observed between serum concentrations of organochlorine compounds in patients with controls and TGCT, but association was observed with serum levels of organochlorines in their mothers during antenatal care, being a predictive factor for increased risk of TGCT in adulthood [70].

#### Gynecomastia

Di (2-ethylhexyl) phthalate (DEHP) is phthalate one of the most commonly used in plastics manufacture. DEHP has been reported as an androgen receptor antagonist. Mono-(2-ethylhexyl) phthalate (MEHP) is known as the first and primary metabolite of DEHP. It was observed that plasma levels of DEHP and MEHP were significantly higher in patients with gynecomastia compared with pubertal controls [71].

## Diagnosis

The diagnosis of androgen deficiency occurs in three stages. Initially should include a general health assessment to look for signs and symptoms of androgen deficiency and exclude systemic disease, eating disorders, and problems of lifestyle, such as excessive exercise or drug abuse. The signs and symptoms of androgen deficiency are nonspecific and are modified by age of

**Table 15.6** Conditions associated with changes in serum SHBG

Decreased concentrations	Obesity
	Nephrotic syndrome
	Hypothyroidism
	Glucocorticoids
	Progestins
	Androgenic steroids
	Acromegaly
Increased concentrations	Diabetes mellitus
	Aging
	Hepatitis and liver cirrhosis
	Hyperthyroidism
	Use of anticonvulsants
	Use of estrogen
	HIV/AIDS

onset, severity and duration of disability, comorbidities, use of androgen sensitivity, and prior therapies. If an androgen deficiency initiated before the patient has completed pubertal development, it often appears as a delayed or incomplete sexual development and eunuchoid proportions (wingspan greater than height by more than 5 cm). In men in whom androgen deficiency develops after complete pubertal maturation, symptoms include reduced sexual desire and activity, reduced spontaneous erections, loss of body hair and reduce the frequency of shaving, infertility, decreased muscle mass and strength, testicles small or shrinking, and breast enlargement. In older men, there may be a background of nonspecific symptoms associated with aging.

Once performed the initial clinical investigation must be dosed serum total testosterone (TT), preferably in the morning and one serum sample using a reliable biochemical assay. An examination with low value should be repeated at least once for confirmation. Measurement of testosterone should be avoided during the period of acute disease since there is suppression of the hypothalamic–pituitary–gonadal resulting in decreased serum levels of TT. Also, conditions which elevate the serum androgen-binding protein (SHBG) decrease the dosage of TT (Table 15.6). The total testosterone measured represents the set of presentations forms of serum testosterone. The absolute value of TT is equal to 2 % free testosterone, 44 % bound to SHBG, and 54 % bound to albumin.

**Table 15.7** Calculation of free testosterone

Vermeulen Formula:  $FT = TT \text{ (nM/L)} / SHBG \text{ (nM/L)} \times 100^{a,b}$

<sup>a</sup>Assuming that the albumin concentration is normal

<sup>b</sup>The calculation of free testosterone, conducted by the formula of Vermeulen, can be obtained at the website: <http://www.issam.ch/freetesto.htm>

FT free testosterone, TT total testosterone, SHBG sex hormone binding globulin

Therefore, it is recommended that the determination of free testosterone (FT) in some individuals, particularly those that have altered levels of SHBG, as in the case of obese patients. The method for analyzing TT considered more accurate and precise is the mass spectrometry. The unavailability in most laboratories, the total testosterone measurement by direct methods and automated (as electrochemiluminescent assay—ECLIA) fulfills its role in most diagnoses [72]. Since most laboratories do not have this methodology and analysis using radioimmunoassay for their evaluation, it is recommended to obtain the values of FT from the construction proposed by Vermeulen, based on the values of TT, SHBG, and albumin (Table 15.7). Other causes of low testosterone levels should be discarded, as hyperprolactinemia, thyroid disorders, chronic diseases, or other disorders. Estradiol should be measured in all adult patients with gynecomastia. DHT is measured in cases of abnormal differentiation of the genitalia and when suspicion of this administration. Semen analysis is of great importance in assessing the individual's fertility and gonadal function [73].

The cutoff points of normal TT for the diagnosis of hypogonadism in adult male is a subject of discussion between different researchers and medical companies. The Endocrine Society (ES) requires TT values below 280–300 ng/dL should be monitored and repeated dosing SHBH for the calculation of FT [74]. The ES recognizes that there is variation in the values of normality ranging between laboratories and according to dosage methodology used. As cutoff calculated free testosterone, American society suggests 5–9 ng/dL. But the consensus established by various medical societies International (International Society of Andrology [ISA], International Society for the Study of Aging



Male [ISSAM], European Association of Urology [UAE], European Academy of Andrology [EAA], American Society of Andrology [ASA]) presents a different proposition [75]. Symptomatic patients with TT dosage above 350 ng/dL do not require androgen replacement. If the value of TT is below 230 ng/dL, the diagnosis of male hypogonadism is executed. However, if the result of TT is the so-called “gray area” (between 230 and 350 ng/dL) is indicated dosage of SHBG and calculation of FT. Are considered hypogonadal patients TL calculated below 6.5 ng/dL. Very low values of TT (below 150 ng/dL) must be further investigated and increases the suspected central or hypogonadism associated with hyperprolactinemia. Recently, Anawalt and coworkers have suggested a new “gray area” for TT between 150 and 400 ng/dL [76].

The third step is to measure the level of LH those allegedly with androgen deficiency to determine whether the fault lies at or in the region testicular hypothalamic–pituitary. Other lab tests and imaging should be evaluated according to each case. On suspicion of testicular diseases, testicular ultrasound can be requested for evaluation of characteristics, location and associated abnormalities. MRI is performed in suspected cases of central nervous system diseases and for the evaluation pituitary in selected cases. Olfactory test must be performed in order to detect the presence of anosmia, hyposmia and as part of the evaluation for Kallmann syndrome. Karyotype is indicated in cases of suspected chromosomal abnormalities as part of hypogonadism. Genotyping for known causes monogenic is currently a research procedure and is not performed in routine clinical practice and may be performed when there is a family history with specific positive or when the patient has phenotypic signs suggestive of a specific mutation. When performed, genetic testing should always be accompanied by genetic counseling.

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## Treatment

The main goal of treatment of patients with hypogonadism is the reestablishment of sexual function and its subsequent maintenance, along with the secondary sexual characteristics and sexual

extra effect of androgens (bone mineral density, muscle hypertrophy, wellness, among others) [77–79]. According to the etiology of hypogonadism, after assessment of fertility of an individual, one can suggest the induction of spermatogenesis, if there is desire fertility.

In the case of primary hypogonadism is diagnosed early, replacement with testosterone is the best option. For congenital secondary hypogonadism, some medical centers recommend starting with gonadotropins to allow the testicles can reach the size of puberty. After testicular growth, the testosterone replacement therapy may be administered until the moment that fertility is desired. Right now, the gonadotropins should be employed in order to design the partner [80]. Antiestrogens may be an alternative therapy, however, their effectiveness has not been adequately tested. In the presence of symptoms of increased estrogen production (gynecomastia and breast tenderness), a short course with the non-aromatizable androgens (dihydrotestosterone, mesterolone, or oxandrolone) may be advisable. However, after a few months of therapy, switching to other preparations aromatizable is recommended to prevent bone loss. When there is concern about the safety of the prostate, the use of steroids or modulators of the androgen receptor nonselective (less susceptible 5 $\alpha$ -reductase) may be advisable. One interesting possibility is to use combined with inhibitors of testosterone 5 $\alpha$ -reductase. Theoretically, binders fraction beta-estrogen receptor could be used, however, the development of these compounds, although promising, are still preliminary search [80].

The major routes of androgen administration [78] are as follows.

## Oral Androgens

The use of prepared 17 $\alpha$ -alkylated (flouximetazona and methyltestosterone) should not be prescribed for its high rate of hepatotoxicity. The ester testosterone undecanoate (40–80 mg, 2–3 times daily) is the only effective as oral administration due to their absorption via the lymphatic system thus minimizing the side effects of its use. Disadvantages: multiple daily doses and variability

in serum hormone. Not been approved for use in the United States of America (USA).

### Transdermal Androgens

Marketed since the 1990s, this form is widespread throughout the world and provides ease of use and provides a close to physiological replacement. Present in the form of gels, adhesives, and non-scrotal scrotal [81].

#### Testosterone Gel (1 %)

Hydroalcoholic formulation, applied in doses of 50–100 mg per day applicable in the body region with low hairiness. Practical and with good tolerability, allowing flexibility in dose with few side effects, mostly limited to local irritation. Disadvantages: potential transfer of the gel to partner through direct contact with skin [81].

#### Testosterone Topical Solution (2 %)

##### Applied to the Axillae

The 2 % formulation of testosterone topical solution, approved by the US Food and Drug Administration (FDA) in November 2010, is a nonocclusive topical formulation administered to the axillae with an applicator instead of the hands. About 5–10 % of the testosterone applied to the axilla is absorbed and appears in serum [82].

#### Transdermal Patches

Both scrotal as the scrotal not be applied once a day, at night. Easy application and ready interrupt if necessary. Less tolerated the gel due to the high rate of local irritation. Need by an area devoid of for adhesion. The application can provide scrotal testicular atrophy light.

### Androgens Injectables

Existing drugs in the market are oily formulations which allow increased dosing interval and the prolongation of the action of testosterone derivative [83, 84].

– *Testosterone cypionate (200 mg ampoules):*

Oil formulation safely administered intramuscularly. Elevates serum testosterone levels, reaching

a peak serum rapidly around the first 2–5 days with mean nadir around the 15–200 day. Allows doses are administered at intervals ranging from 2 to 4 weeks, depending on the clinical response of the patient. Advantage: fewer applications, low cost, and easy access. Disadvantage: not mimic physiological hormonal cycle, with supra-physiological levels achieved in the first days after application.

– *Testosterone esters (ampoules containing 250 mg of 4 esters: propionate, phenylpropionate, testosterone decanoate and isocaproate):*

And also oily formulation administered intramuscularly. The mixture of four kinds of testosterone esters with proportions and different peaks of activity confers hormone peaks at different times. Try to avoid peak supra-physiological initial cycle and promote a closer to normal. The advantages and disadvantages are similar to testosterone cypionate.

– *Undecylate (or undecanoate) Testosterone (ampoules 1,000 mg):*

Oil formulation and administration intramuscularly, using as the castor oil vehicle. Shows no peak action and its action is longer, keeping close to physiological levels for a period of 10–14 weeks. At the time of the first application range for the second dose should be 6 weeks and has settled down after a mean interval between doses of 12 weeks, individually adjusted according to clinical response and laboratory. Advantages: mimicry to normal hormonal cycle, longer duration of action of application, and convenience in dosing. Disadvantage: high cost.

#### Subcutaneous Implants

In the form of pellets are implanted subcutaneously. The dose and regimen vary with the formulation used, but generally have duration of action of about 3–6 months and the dose varies between 150 and 450 mg. Disadvantages: local complications, discomfort, infection at the site of application, and the possibility of extrusion of the *pellet*. Advantage: Dosage of long-term use.

#### Other Forms of Reset

Adhesive oral 30 mg applicable gum twice a day [85]. Another option is the hCG. Although not an androgen, stimulates the testes to produce

testosterone and is especially useful when one wishes to stimulate the production of sperm and hence male fertility.

### Male Hypogonadism Associated with T2DM and Obesity: To Treat or Not To Treat?

Only in the last decade, the main consensus on male hypogonadism started adding conditions between DM2 risk of decreased testosterone, calling attention to the need for treatment of these patients [74, 75]. The TIMES2 Study is an important work that evaluated hypogonadal patients with T2DM and metabolic syndrome. Their results show a significant decrease in HOMA-IR among hypogonadal diabetic patients after 6 months of testosterone replacement gel and a better control of HbA1c after 9 months treatment [86]. Helfelder et al. evaluated hypogonadal men with newly diagnosed type 2 diabetes treated with testosterone and change in lifestyle (CL) compared to placebo and CL. After 52 weeks, testosterone replacement resulted in better control of HbA1c and significant reduction in abdominal waist (14.6 cm vs. loss of 6.7 cm, respectively) [87].

A number of studies demonstrated that treatment of hypogonadism improves weight loss of hypogonadal obesity. Svartberg et al. found in a case-control study of an improvement in body shape of elderly hypogonadal men treated with testosterone for 1 year [88]. The study evaluated 184 Moscow hypogonadal men with metabolic syndrome [89]. After 30 weeks of administration of parenteral testosterone undecanoate, significant drop in weight, BMI, and waist circumference, as well as improving some components of MS and inflammatory markers [89].

Thus, treatment of hypogonadism in obese men can be effective in helping weight loss because it improves energy and mood, reduces fatigue and may motivate men to adhere to diet and exercise are fundamental in combating obesity [90].

### Monitoring and Follow

In adolescent or young adult patients, the prostate is not a concern. However, in older men, especially after age 40, the prostate should be moni-

**Table 15.8** Conditions in which testosterone replacement is associated with high risk of adverse events and should be contraindicated

High risk of adverse events (absolute contraindication)	Metastatic prostate cancer or activity Breast cancer
Moderate risk of adverse events (relative contraindication)	Palpable nodule or induration prostate Prostate-specific antigen (PSA) greater than 4 ng/mL or undiagnosed urological treatment (or greater than 3 ng/mL in subjects at high risk for prostate cancer, as afro-american or men with first-degree relatives with a history prostate cancer) Hematocrit above 50 % Obstructive sleep apnea severe untreated Severe symptoms with a urinary tract (International Prostate Symptom Score above 19) Heart failure uncontrolled or poorly

tored. Currently, it is known that testosterone replacement does not cause the appearance of prostate cancer in patients who do not have a background for it. However, testosterone and mainly dihydrotestosterone can stimulate prostate tissue [91]. In the last decade, some case series described the use of testosterone therapy in hypogonadal men after treatment for prostate cancer and no clinical or biochemical progression of the tumor. This is not yet an established practice at the time, but it indicates a possible security in these cases.

It is not recommended initiation of testosterone therapy in men with breast cancer or prostate cancer, with a palpable nodule or indurations or prostate with prostate-specific antigen (PSA) greater than 4 ng/ml or undiagnosed urological treatment, hematocrit above 50 %, obstructive sleep apnea, severe untreated, severe urinary tract symptoms with a score of prostate symptom (International Prostate symptom Score) over 19, heart failure or uncontrolled or poorly controlled (Table 15.8) [74].

When testosterone therapy is instituted, one should achieve the average normal levels of testosterone during treatment with any of the

**Table 15.9** Monitoring testosterone therapy

1. Evaluate the patient 3–6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects
2. Monitor testosterone level 3–6 months after initiation of testosterone therapy
Therapy should aim to raise serum testosterone level into the mid-normal range
<i>Injectable testosterone enanthate or cypionate</i> : measure serum testosterone level midway between injections. If testosterone is >700 ng/dl (24.5 nmol/l) or <400 ng/dl (14.1 nmol/l), adjust dose or frequency
<i>Transdermal patches</i> : assess testosterone level 3–12 h after application of the patch; adjust dose to achieve testosterone level in the mid-normal range
<i>Buccal testosterone bioadhesive tablet</i> : assess level immediately before or after application of fresh system
<i>Transdermal gels</i> : assess testosterone level any time after patient has been on treatment for at least 1 week; adjust dose to achieve serum testosterone level in the mid-normal range
<i>Testosterone pellets</i> : measure testosterone levels at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range
<i>Oral testosterone undecanoate<sup>a</sup></i> : monitor serum testosterone level 3–5 h after ingestion
<i>Injectable testosterone undecanoate</i> : measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone in mid-normal range
3. Check hematocrit at baseline, at 3–6 months, and then annually. If hematocrit is >54 %, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinstitute therapy with a reduced dose
4. Measure bone mineral density of lumbar spine and/or femoral neck after 1–2 year of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care
5. In men 40 year of age or older with baseline PSA greater than 0.6 ng/ml, perform digital rectal examination and check PSA level before initiating treatment, at 3–6 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient
7. Obtain urological consultation if there is
An increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment
A PSA velocity of >0.4 ng/ml year using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 year)
Detection of a prostatic abnormality on digital rectal examination
An AUA/IPSS of >19
8. Evaluate formulation-specific adverse effects at each visit
<i>Buccal testosterone tablets</i> : inquire about alterations in taste and examine the gums and oral mucosa for irritation
<i>Injectable testosterone esters (enanthate, cypionate, and undecanoate)</i> : ask about fluctuations in mood or libido, and rarely cough after injections
<i>Testosterone patches</i> : look for skin reaction at the application site
<i>Testosterone gels</i> : advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact, because testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. Serum testosterone levels are maintained when the application site is washed 4–6 h after application of the testosterone gel
<i>Testosterone pellets</i> : look for signs of infection, fibrosis, or pellet extrusion

<sup>a</sup>Not approved for clinical use in the USA

formulations adopted. The choice of formulation of testosterone must take into account the patient's preference, the pharmacokinetics, and cost. Men receiving testosterone therapy should be monitored continuously through a standardized plan that includes medical consultation with a physical examination and laboratory tests (PSA and hematocrit) (Table 15.9) [74].

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# Idiopathic Short Stature: Diagnostic and Therapeutic Approach

# 16

Ana P.M. Canton and Alexander A.L. Jorge

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## Case report

Our clinical case for discussion is about a short statured boy who was 14.6 years old at his first evaluation. He was born after a 39-week gestation as the third child of a non-consanguineous marriage. His birth weight was 3.250 g (−0.3 SDS), and his birth length was not available. His neuropsychomotor development was normal, his school performance was good, and there were no remarkable findings in his medical history. His father's height was 174 cm (−0.1 SDS) and his mother's height was 154 cm (−1.3 SDS), resulting in a target height of 170.6 cm (−0.6 SDS). His father and mother apparently had normal pubertal

development, and his mother's age of menarche was 13 years old. His older brother's height was not available, but he had a previous history of pubertal spurt after 16 years of age. Likewise, his older sister's height was also not available, but she had a previous history of menarche at 14.

At the presentation, the height of the patient was 142.5 cm (−2.6 SDS), his weight was 29.4 kg (−3.9 SDS), his body mass index was 14.5 kg/m<sup>2</sup> (−3.1 SDS), and his sitting height was 73 cm (−0.3 SDS). Physical examination was unremarkable, without dysmorphic features. His pubertal staging was G2P1, as determined by Marshall & Tanner criteria. His bone age was 11 years old, as determined by Greulich & Pyle criteria. At this moment, his adult height prediction was 173.1 cm (−0.2 SDS), as determined by the Bayley–Pinneau method.

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## Introduction

Growth is an essential process for the development of a healthy adult and it is a sensitive marker of child health status. It comprises a dynamic, non-homogeneous, and complex process of replication and differentiation of cells from several tissues [1]. It is generally assumed that growth is regulated by a multitude of genetic and epigenetic mechanisms, which interact with influences from internal and external environments. With respect to genes, it is assumed that both adult height and growth pattern are largely genetically programmed [2].



Growth intensity differs depending on the stage of life, from intrauterine to adult life. During the prenatal period, growth velocity varies greatly according to gestational age, with a median growth of 1.2–1.5 cm per week. In late gestation, growth velocity takes on a process of deceleration that persists until pubertal onset. In the first and second years of life, children's growth velocity is, in average, 25 and 12 cm/year, respectively. After that, it decelerates gradually to an average of 4–6 cm/year until the pubertal spurt starts. During puberty, there is an acceleration of growth, and children can reach an average height velocity (HV) of 12 cm/year. Pubertal spurt onset time is dependent on the age children start puberty. Girls start a rhythm of growth acceleration in the early pubertal development, while boys start this same process in the late pubertal development [3].

Growth disorders are associated with different diseases, which encompass different systems and mechanisms. Therefore, short stature is one of the most common concerns presented to pediatric endocrinologists and other child-caring physicians. Despite the complexity of the matter, some diagnoses can be obtained by a careful analysis of medical history and a comprehensive physical examination [1, 4].

In this chapter, we present referral criteria for children with short stature, diagnostic procedures to detect the causes of this condition, involved differential diagnosis, and possible therapeutic approaches. Idiopathic short stature diagnosis and approach will be specifically emphasized.

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## Short Stature Diagnosis

### Criteria for Investigation of Short Stature

Height has an almost perfect Gaussian distribution in large-scale growth studies. Therefore, the first key point in the diagnostic approach of children with short stature is the application of referral criteria for diagnostic workup. With this application we can distinguish if they are simply within the shortest part of the “normal” distribu-

tion or if they effectively are with a disorder restricting growth [2].

In the initial evaluation of growth, there are basically three parameters that can be assessed. First, height can be compared with age and sex references and expressed as standard deviation score (SDS) or centile position. Height SDS is a measure of the deviation of the individual height from the mean and is expressed as the number of standard deviation below or above the mean height of the population for the same age and sex [5]. Therefore, by definition, individuals are defined as short statured when they present a height SDS < -2.0 or a height below the 2.3 % percentile for a given age, sex, and population.

Second, height SDS can be compared with the sex-corrected parental height (target height) SDS [5]. The target height is a mathematical calculation, which expresses the genetic potential of height of an individual. It can be calculated by the arithmetic mean of parental height with the addition or subtraction of 6.5 cm for boys and girls, respectively [1, 3]. Children should be referred for a diagnostic workup when he/she is “short for the target height,” i.e., when the height SDS minus target height SDS is below -2.0.

Third, a longitudinal analysis of growth can be used, either expressed as height velocity (cm/year or SDS) in comparison to age and sex references or as a height SDS change (deflection or deviation) from the original SDS position (height SDS change is the difference in height SDS between two measurements, preferably 1 year apart from each other) [5]. A growth deflection (or a “crossing” of height percentiles) is defined as a height SDS decrease > 1 SD and should also be considered abnormal requiring further evaluation.

### Diagnostic Approach

Short stature can be the presenting symptom or the suggestive symptom of numerous conditions and diseases. There are different classifications for its differential diagnosis, but most of them include three main groups: primary short stature (skeletal abnormalities), secondary short stature, and short stature without recognizable

**Table 16.1** Differential diagnosis in short stature

<i>Primary short stature</i> —Skeletal abnormalities
With recognizable skeletal dysplasia (achondroplasia, hypochondroplasia)
Without recognizable skeletal dysplasia (Turner syndrome, <i>SHOX</i> gene haploinsufficiency)
<i>Secondary short stature</i>
Malnutrition
Psychosocial deprivation
Chronic diseases
• Renal (renal failure, tubular acidosis, nephrotic syndrome)
• Intestinal (celiac disease, intestinal inflammatory disease)
• Hematological (chronic anemia)
• Cardiac
• Pulmonary (cystic fibrosis)
• Endocrine
◦ Hypothyroidism
◦ Disorders of the GH/IGF-1 axis
◦ Cushing's syndrome
◦ Pseudohypoparathyroidism
◦ Rickets
<i>Short stature without recognizable cause</i>
Intrauterine growth retardation without recognizable cause (small for gestational age with failure of catch-up growth)
Idiopathic short stature
• Familial short stature
• Constitutional delay of growth and puberty
GH growth hormone, <i>IGF-1</i> insulin-like growth factor type 1

cause (Tables 16.1 and 16.2). The latter group includes the diagnosis known as idiopathic short stature (ISS).

Clinical evaluation starts with a detailed medical and family history and a thorough physical examination (Table 16.3). A keypoint is a detailed description of the child's growth pattern, including the time when the growth deficit was first observed. Birth characteristics must be evaluated (gestation and delivery conditions or complications; gestational age, birth weight, length and head circumference). This information is important to distinguish short children in two groups by the onset of the growth impairment: short stature with prenatal or postnatal onset. Medical history must be investigated, with a focus in neuropsychomotor development, nutritional status, medi-

**Table 16.2** Disorders of the GH/IGF-1 axis

<i>GH deficiency</i>
Idiopathic
Acquired (craniopharyngioma, pituitary tumors, autoimmune diseases, granulomatous diseases, central nervous system infections, head trauma)
Genetic
• GH secretion ( <i>GHI</i> and <i>GHRHR</i> genes)
• Pituitary cells differentiation ( <i>POU1F1</i> and <i>PROPI</i> genes)
• Pituitary development ( <i>HESX1</i> , <i>GLI2</i> , <i>LHX3</i> , <i>LHX4</i> , and <i>SOX3</i> genes)
<i>Bioinactive GH</i>
<i>GHI</i> gene mutation
<i>GHInsensitivity</i>
Primary
• Laron syndrome ( <i>GHR</i> gene)
• Associated to immunodisfunction (abnormalities of GH signal transduction, e.g., <i>STAT5B</i> gene defect)
Secondary or acquired (AntiGH antibodies, malnutrition, liver disorders, diabetes mellitus poorly controlled, uremia)
<i>Ternary complex formation deficiency (IGF-1/IGFBP-3/ALS)</i>
Acid-labile subunit deficiency ( <i>IGFALS</i> gene)
<i>IGF-1 deficiency</i>
<i>IGF1</i> gene
<i>Bioinactive IGF-1</i>
<i>IGF1</i> gene mutation
<i>IGF-1 insensitivity</i>
<i>IGF1R</i> defects and post receptor defects
GH growth hormone, <i>IGF-1</i> insulin-like growth factor type 1, <i>IGFBP-3</i> insulin-like growth factors binding protein 3, <i>ALS</i> acid-labile subunit

cation use, and cardiac, renal, pulmonary and gastrointestinal diseases. Evaluation of a child's height must take into account the familial patterns of growth and puberty [1].

Physical examination should be complete, including the description of anthropometric measurements, facial and body dysmorphic features, and any other clues for one of the many causes of short stature. In children younger than 2 years of age, supine length, weight, weight-for-length, and head circumference will be measured, and fontanelles as well as dentition should be evaluated. In older children, erect height, weight, body mass index (BMI), head circumference, arm span, and sitting height (SH) should be measured [1].

**Table 16.3** Specific diagnostic findings and keypoints in medical history and physical examination of children with short stature

Findings and keypoints	Interpretation and application
<i>Medical History</i>	
Birth length, weight, head circumference, gestational age	Classification as SGA or AGA
Previous growth data	Height velocity and growth pattern analysis
Age at start of pubertal signs	Early, normal, or delayed puberty
Previous diseases, surgeries, and medication use	Organic or iatrogenic causes
Medical history of the various systems	Search for chronic and systemic diseases
Feeding and nutrition history	As example, Silver–Russell and Prader–Willi syndromes can lead to feeding difficulties
Neuropsychomotor development delay and/or intellectual disability	Syndromes, chromosomal disorders, metabolic disorders
Consanguinity	Likelihood of recessive genetic disorders
Parental height (measured)	To estimate the target height
Parents' age at the start of puberty	To assess likelihood of a familiar pattern of delayed puberty
<i>Physical Examination</i>	
Length or height, weight, head circumference, sitting height, arm span, forearm length	Altered sitting height–height ratio is suggestive of skeletal dysplasia
Weight-for-height or BMI showing underweight	Weight more affected than height, low weight-for-height and low BMI are suggestive of malnutrition
Weight-for-height or BMI showing overweight or obesity	Hypothyroidism, Cushing's syndrome, GH deficiency, pseudohypoparathyroidism
Dysmorphic features	Syndromes
Pubertal stage	Early, normal or delayed puberty
General physical exam	Search for chronic and systemic diseases

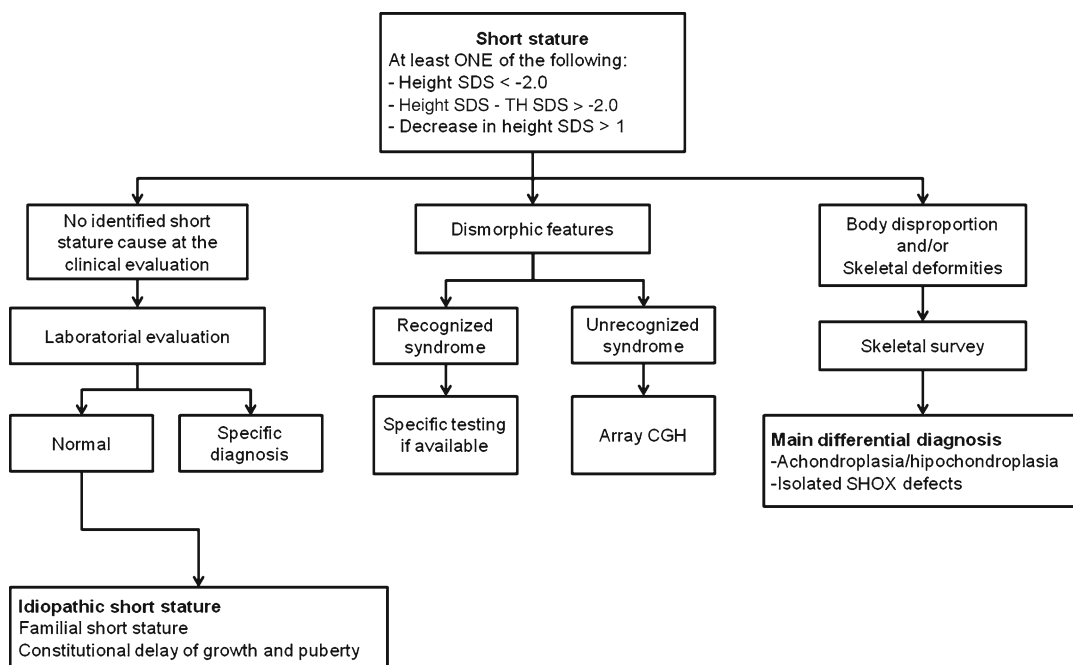
SGA small for gestational age, AGA adequate for gestational age, IUGR intrauterine growth retardation, BMI body mass index, GH growth hormone, IGF-1 insulin-like growth factor type 1, CNS central nervous system

In the latter, the pubertal staging has to be evaluated, as determined by Marshall and Tanner criteria [6, 7]. Evaluation of a child's height must be done in the context of normal standards for sex and age with the international data at hand. Such standards can be either cross-sectional (by calculation of height SDS) or longitudinal (by plotting in growth charts). Serial measurements with a minimum interval of 6 months are necessary to determine the height velocity. Because genetic factors are important determinants of growth and height, all children should be assessed considering siblings and parents. For that purpose, the parental target height is calculated and expressed as mentioned above. When a child's growth pattern clearly deviates from that of parents and siblings, the possibility of an underlying pathology should be considered [3].

Many abnormal growth states are characterized by disproportionate growth, which is strongly

suggestive of skeletal dysplasia. Therefore, body proportion measurements should be part of the evaluation of short stature. We recommend the use of sitting height: height ratio (SH:H) for age and sex, which can also be expressed in SDS, according to published standards. This ratio allows for the observation of body proportion changes throughout development. Children with short stature and an increased SH:H ratio for age and sex have a disproportional short stature caused by limb abnormalities, while children with short stature and a decreased SH:H ratio for age and sex have a disproportional short stature caused by axial segment abnormalities [1, 8] (Fig. 16.1).

Depending on specific clinical clues at medical history and physical examination, special investigations are required. When skeletal dysplasia is suspected, skeletal survey analysis is indicated for a more precise diagnosis, includ-



**Fig. 16.1** Diagnostic approach in children with short stature. SDS=standard deviation score; TH=target height; CGH=comparative genomic hybridization

ing the following parts: skull, spine, pelvis, upper limb, and lower limb (Fig. 16.1) [9]. Likewise, when dysmorphic features are suggestive of syndromic causes, diagnostic investigations have to prioritize them. It is generally advised to request a karyotype in short girls, even in the absence of typical signs of Turner syndrome.

When clinical evaluation does not point to a diagnosis, initial laboratorial and radiographic screening must include a wide group of diseases that can be associated with short stature (Fig. 16.1 and Table 16.4). It is assumed by most groups that a radiograph of the left hand and wrist is a useful adjunct. On this radiograph, bone age can be determined by comparison with the normal age and sex-related standards published by Greulich and Pyle [10]. Skeletal maturation can be used to predict adult height. The most commonly used method for height prediction is the Bayley and Pinneau method [11].

One of the most important parameters to be evaluated is the growth hormone/insulin-like

growth factor-1 (GH/IGF-1) axis. There are several defects that affect this axis (Table 16.2) and, among them, growth hormone deficiency (GHD) is the most prevalent. However, the latter is responsible for only 5 % of short stature cases.

Laboratorial investigation of GHD is made by direct and/or indirect analysis of the GH secretion. The direct analysis is made by provocative tests (also called stimulation tests), and pharmacological ones are the most appropriate. The most important tests are insulin, clonidine, arginine, and glucagon, which are comparable in terms of sensitivity and specificity. The choice of a test to provoke GH secretion is dependent on the center experience and on the test availability. From 10 to 35 % of short statured children without GHD may have an inadequate response to one test. Because of this, two provocative tests must be made for GHD diagnosis [12] (Fig. 16.2). Another important topic related to provocative tests is the use, or not, of sexual steroid priming. It is well known that the peak of GH level after a stimulation test is higher if the patient has been

**Table 16.4** Initial laboratorial and radiographic screening in diagnostic workup of short stature

Exam	Objective (to detect or exclude)
Blood cells count, erythrocytes sedimentation rate	Anemia, infections, chronic inflammatory diseases
Albumin, ferritin	Poor nutritional status
AST, ALT, $\gamma$ GT	Chronic liver diseases
Creatinine, sodium, potassium, venous blood gas analysis, urinalysis	Renal disorders, renal tubular acidosis <sup>a</sup>
Calcium, phosphate, alkaline phosphatases	Calcium/phosphate disorders
IgA-anti-endomysium antibodies, IgA-anti-tissue transglutaminase antibodies and total IgA	Celiac disease
Parasitological analysis	Worm infections
TSH and Free T4	Thyroid disorders
GH, IGF-1, and IGFBP-3	GH/IGF-1 axis disorders
Karyotype	Turner syndrome
Radiograph of the left hand and wrist	Bone age
Skeletal survey analysis (skull, spine, pelvis, upper limb and lower limb, in two views)	Skeletal dysplasias

<sup>a</sup>Renal tubular acidosis should be excluded in children younger than 4 years old with short stature and difficulty in gaining weight

*TSH* thyroid stimulating hormone, *free T4* free tetraiodothyronine, *GH* growth hormone, *IGF-1* insulin-like growth factor type 1, *IGFBP-3* insulin-like growth factors binding protein 3

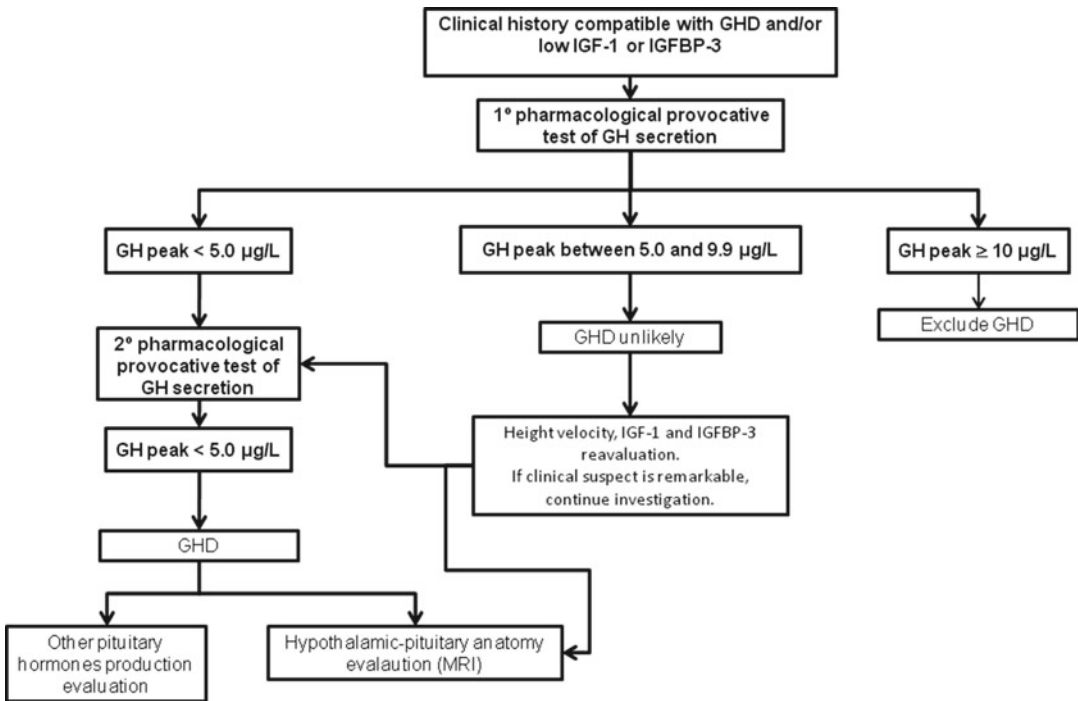
recently exposed to sex steroids. Some authors suggest that priming should be used mainly in children with pubertal delay. Controversy regarding this practice persists [13].

The indirect analysis of the GH secretion is made by serum concentrations of IGF-1 and insulin-like growth factors binding protein 3 (IGFBP-3). Both of them are directly related to GH action and are used as screening tests to select short statured children for GHD diagnostic tests. The IGF-1 and IGFBP-3 serum levels vary with age, sex and pubertal staging. When the hormonal diagnostic is established, a hypothalamic–pituitary magnetic resonance (MRI) is requested for anatomical evaluation [12] (Fig. 16.2).

## Case Report Evolution and the Diagnosis of Idiopathic Short Stature (ISS)

Continuing our clinical case discussion, we can conclude that the boy met the referral criteria to initiate diagnostic workup: height SDS  $-2.6$  ( $<2.5$ ) and height below target height (difference of 2.0 SD). Laboratory analyses, including blood cells count, erythrocytes sedimentation rate, creatinine, sodium, potassium, calcium, phosphate, alkaline phosphatase, venous blood gas analysis, ferritin, albumin, AST, ALT,  $\gamma$ GT, IgA-anti-endomysium antibody, TSH, free T4, urinalysis, and parasitological analysis were all normal. As the patient presented a proportional short stature (SH:H SDS of  $-0.3$ ), skeletal survey analysis was not performed. Likewise, as he did not present dysmorphic features, karyotype or other diagnostic investigations for specific syndromic causes were not necessary. Serum concentrations of IGF-1 and IGFBP3 were both  $<-2.0$  SDS. As such, a clonidine test was performed, but the GH peak after the pharmacological stimulus was  $17 \mu\text{L}$ , ruling out GHD.

At this moment, we had excluded the most recognizable diseases associated with short stature, and we formulated a hypothesis of idiopathic short stature (ISS). The term ISS does not reflect an exactly defined diagnosis. It is usually used for children whose shortness compared to age-matched normal population cannot be attributed to specific diseases [14]. According to the Consensus Statement on the diagnosis of ISS, “it is defined as a condition in which the height of an individual is more than 2 SDS below the corresponding mean for height for a given age, sex and population group, without evidence of systemic, endocrine, nutritional or chromosomal abnormalities; it describes a heterogeneous group of children consisting of many presently unidentified causes of short stature” [4]. It is estimated that 60–80 % of all short children presented to pediatric or endocrinological evaluation can be labeled according to this definition. ISS can be subcategorized. The main distinction is between



**Fig. 16.2** Investigation protocol of children with suspected GHD. GH=growth hormone; GHD=growth hormone deficiency; IGF-1=insulin-like growth factor type 1;

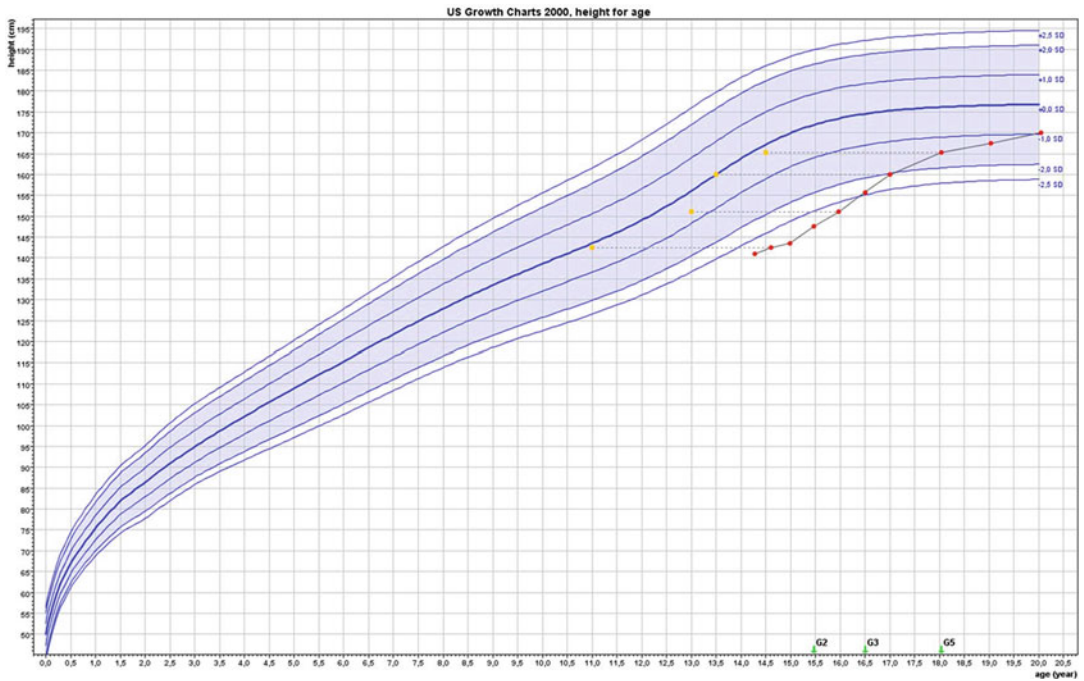
IGFBP-3=insulin-like growth factors binding protein 3; MRI=magnetic resonance

children with a familial history of short stature (familial short stature, FSS) and those children who are short for their parents (non-familial short stature, non-FSS) [4]. In FSS, children are short compared with the relevant population but remain within the expected target range for the family. In non-FSS, children are short for the population as well as for the target range. In addition, ISS children can also be subcategorized according to the age of puberty onset, presenting a constitutional delay of growth and puberty (CDGP). The diagnosis of CDGP is based on lack of breast development (Tanner stage 2) by the age of 13 in girls and testicular volume <4.0 ml by the age of 14 in boys, absence of other identifiable causes of delayed puberty, delayed bone age (BA), as well as spontaneous and complete achievement of pubertal development during follow-up [2].

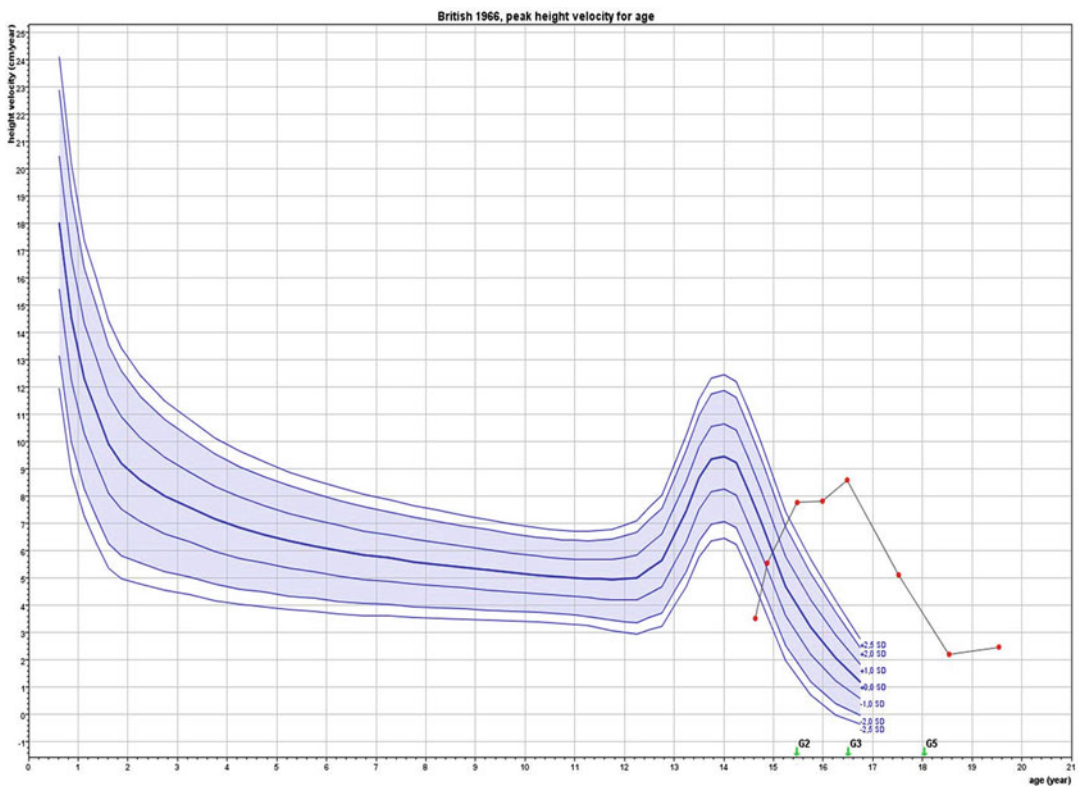
In the presenting case, we could classify the patient with a non-familial proportional short stature of postnatal onset. And, because he presented a remarkable bone age delay and a

delayed puberty, the most appropriate hypothesis was CDGP. The patient was evaluated every 6 months, when the auxological data were repeatedly measured (Fig. 16.3). He started puberty at the age of 15. His bone age was 12 years and at that time height velocity increased from 3.7 to 5.1 cm/year. The peak height velocity was 8.8 cm/year, observed at 16.5 years old and pubertal staging G4P3 (Fig. 16.4). At 17.5 years old, his height was 165.3 cm (−1.4 SDS), his bone age was 14.5 years, his pubertal staging was G5P5, and his adult height prediction was 174.3 cm (0.0 SDS). At 20 years old, he reached his final height (or adult height) in 170 cm (−0.7 SDS) (Figs. 16.3 and 16.4).

The case report above mentioned is a common example in clinical practice. It brings out two important points in the management of patients with ISS. First, ISS is not a diagnostic entity in terms of etiology or pathogenesis. It is a term used to describe such forms of growth failure that cannot be attributed to any known cause of



**Fig. 16.3** Height for age growth chart of the patient presented. *Red marks*=height measures in follow-up visits; *yellow marks*=bone age as determined by Greulich and Pyle criteria; G2, G3, and G5=pubertal stages 2, 3, and 5, respectively, as determined by Marshall and Tanner



**Fig. 16.4** Height velocity for age growth chart of the patient presented. *Red marks*=height velocity measures in follow-up visits; G2, G3, and G5=pubertal stages 2, 3, and 5, respectively, as determined by Marshall and Tanner

short stature and are usually considered normal variants of growth [14]. Secondly, the choice between using or not growth-promoting therapies has to take into account the natural history and the growth pattern of children with ISS.

Several studies have been published about the natural history of ISS. In most of them, it is assumed that FSS and CDGP are different. Children with FSS tend to be younger at presentation of short stature; reach an adult height SDS similar to the initial height SDS and reach the target height more precisely than the predicted adult height. Conversely, children with CDGP tend to be older at presentation; reach an adult height SDS higher than initial height SDS and more compatible with predicted adult height based on bone age [2, 14].

In an important study evaluating the spontaneous adult height in ISS, Ranke et al. found that 67 % of children with FSS reached adult height within the normal range, whereas 81 % of children with CDGP reached it as well. As a group, only 5 % of children with ISS did not reach an adult height above  $-2.0$  SDS, thus becoming short adults. Moreover, 10 % of children with ISS did not reach an adult height within the range of their target height. In clinical observation of the natural history of ISS, there are three main indicators of a poor adult height outcome: younger age at presentation, lower target height and lower predicted adult height at presentation (as measured by BP method) [14]. Once aware of the spontaneous growth pattern of children with ISS, growth-promoting therapies to improve final height are no longer widely justified.

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## Present Therapies for Short Stature

When a specific disease is known to be the cause of growth retardation, the treatment of this condition is considered the best therapy for short stature. Current available treatments, used for different causes of short stature, are recombinant human GH (rhGH), recombinant human IGF-1 (rhIGF-1), gonadotropin-releasing hormone analogs (GnRHa), and aromatase inhibitors.

The rhGH is the main hormonal treatment of short stature and is accepted as a safe and effec-

tive therapy. Presently, according to the US Food and Drug Administration (FDA), the indications for its use are: GHD, small for gestational age (SGA), Turner syndrome, Prader–Willi syndrome, chronic kidney disease, *SHOX* gene haploinsufficiency, Noonan syndrome, and ISS. According to the European Medicines Agency (EMA), indications are the same, except for Noonan syndrome and ISS, which are not included. Several studies assessed different variables which can influence final height after rhGH therapy in children with different conditions. Duration of treatment, height at the start of treatment, bone age delay, height at puberty onset, midparental height, and first year of treatment growth velocity were positively correlated, whereas age at the beginning of treatment had a negative correlation [1, 2].

GHD is the most accepted indication for rhGH treatment. In these cases, the reposition of physiological doses of GH ( $33 \mu\text{g}/\text{kg}/\text{day}$ ) allows for growth normalization and should be initiated as soon as the diagnosis is established [15]. Children with severe GHD have higher height velocity in initial treatment and greater height gain in overall treatment than other causes of short stature. When initiated early, GH reposition results in adult height close to target height [16].

The use of rhGH to increase adult height in ISS is controversial. Most studies indicate that height velocity increases in short term and that final height gain is modest, with a mean increase of 4 cm [17]. GH therapy should not be used indiscriminately in ISS. Most studies do not show sufficient evidence with respect to safety and psychosocial benefits in this condition. Moreover, studies about the natural history of ISS show that most children become normal adults with adequate stature outcome, even without treatment [14]. In addition, in children with ISS, there is a great interindividual variability in the response to GH therapy, and there are no effective tools to predict the individual response. The treatment has a high cost and is not completely free of adverse effects. For these reasons, in ISS, rhGH use should be restricted to very important short stature (height SDS  $< -3.0$  and low height velocity) and should be done under the supervision of specialized groups [1].



Besides rhGH, alternative growth-promoting therapies have been assessed in ISS as well as in other causes of short stature. Some studies evaluated the use of GnRHa, with or without concomitant rhGH in short stature. Those that kept the agonists for 3 or more years showed a modest final height gain in children with GHD, ISS, and SGA [18–20]. However, the consequences of its use in long terms are still unclear. Recently, the use of aromatase inhibitors, capable of inhibiting the conversion of testosterone in estradiol, has been evaluated in boys with short stature. The results were promising but still experimental [21]. Recombinant human IGF-1 is the treatment of choice in children with primary or secondary forms of GH insensitivity, and its use should be restricted to these conditions.

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## Key Points to the Diagnosis

There are a wide range of conditions that can present with a delay in puberty [1], making a systematic tapered approach fundamental to the diagnostic process. In considering a patient with delayed puberty, the most important initial assessment is the gonadotropin status. Disorders of pubertal delay can be broadly categorized into hypogonadotropic, hypergonadotropic, and eugonadotropic hypogonadism (Table 17.1).

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## Introduction

Puberty is initiated when the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator begins secreting brief nocturnal pulses of GnRH from the hypothalamic arcuate nucleus that subsequently stimulate the pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [2]. A recently dis-

covered hormone, kisspeptin, acts on the hypothalamic GnRH neurons, stimulating GnRH secretion [3]. The gonadotropins (LH and FSH) promote gonadal maturation and gonads synthesize sex steroids, including testosterone and estrogen, and other proteins. LH acts on theca cells and interstitial cells to produce progesterins and androgens which diffuse into adjacent granulosa cells. FSH acts on granulosa cells to stimulate aromatization of these androgens to estrogen. Estrogen and testosterone then promote pubertal changes throughout the body and provide negative feedback effect on the GnRH and gonadotropins (Fig. 17.1). The first physical signs of puberty are typically breast development in girls and testicular enlargement in boys (testicular volume  $>3$  ml/ $\geq 2.5$  cm in length). Some children, especially girls, have the appearance of pubic hair prior to the initiation of breast development, but in the absence of other puberty signs this usually represents adrenarche [adrenal source of androgens, independent of hypothalamic–pituitary–gonadal (HPG) axis maturation] and not true puberty. The trigger(s) for reactivation of the HPG axis is not completely understood; but, modifying factors include general health, nutrition, genetic determinants, and pubertal timing among primary relatives. Elevated body mass index is associated with delayed puberty in boys [4, 5]. Many of the genes involved in the HPG axis maturation are still unknown. Kisspeptin-1 and its cognate receptor (GPR54, a G-protein-coupled receptor) are integral to the normal function of HPG axis and play a critical role in

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**Table 17.1** Etiology of delayed puberty

## Hypogonadotropic hypogonadism (low LH and FSH)

- Constitutional delay of growth and puberty (CDGP)
- Functional hypogonadotropic hypogonadism: Delayed, but spontaneous, pubertal development
- Permanent idiopathic hypogonadotropic hypogonadism (IHH)

*Hypothalamic and pituitary dysfunction*

- CNS tumors: Germinoma, optic glioma, oligodendroglioma, Rathke's pouch/cleft cyst astrocytoma, pituitary tumor
- Panhypopituitarism
- Isolated gonadotropin deficiency
- Hypophysitis
- Langerhans histiocytosis
- Radiation therapy
- Head trauma
- Congenital malformation with midline central defect (Septo optic dysplasia)
- Mutations in the *PROPI*, *LHX3*, and *HESX1* genes

Syndromes: Prader–Willi syndrome, Coffin–Lowry syndrome, CHARGE syndrome, Laurence–Moon–Biedl syndrome, and others

Mutations in the *NR0B1*, *GPR54* genes, GnRH receptor gene mutations, inactivating mutations of *KISS 1* and *KISS 1 R* genes, loss-of-function mutations in genes encoding *neurokinin B* and its receptor, DAX-1 mutations

## Hypergonadotropic hypogonadism (increased LH and FSH)

- Gonadotropin receptor mutations
- FSH  $\beta$  subunit gene mutation
- LH/FSH receptor mutation
- Gonadal dysgenesis
- Turner syndrome
- Premature ovarian failure
- Resistant ovary syndromes
- Irradiation
- Cytotoxic therapy
- Trauma
- Infections
- Galactosemia
- Glycoprotein syndrome type I
- AIS with gonadectomy
- Androgen resistance

## Eugonadotropic hypogonadism (normal LH and FSH)

## Steroidogenic enzyme defects

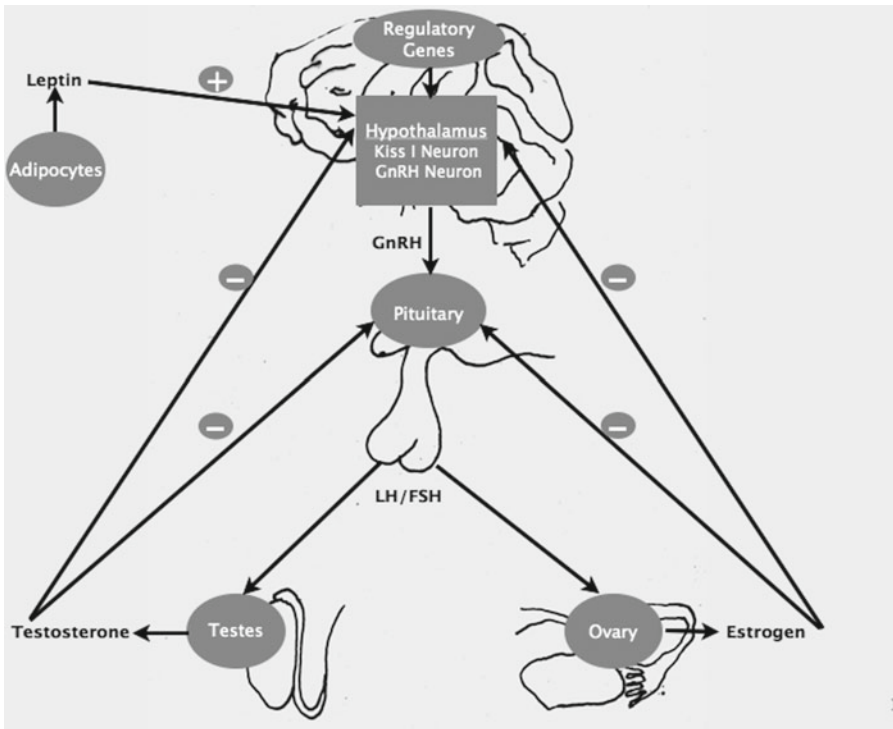
- Cholesterol desmolase complex deficiency (lipoid adrenal hyperplasia)
- 3- $\beta$  OH-steroid dehydrogenase deficiency
- 17  $\alpha$ -hydroxylase deficiency
- C17,20-desmolase deficiency
- 17- $\beta$  OH steroid oxidoreductase deficiency
- 21-hydroxylase deficiency in girls

## Anatomic abnormalities

- Imperforate hymen
- Vaginal atresia
- Vaginal and uterine agenesis (Mayer Rokitansky–Kuster–Hauser syndrome)

## PCOS

## Prolactinoma



**Fig. 17.1** Schematic illustration of pubertal regulation, demonstrating the factors and hormones providing positive and negative feedback control

the physiologic regulation of puberty [3, 6]. Kisspeptin is co-expressed with neurokinin B and dynorphin and hence these signaling pathways are also important in physiologic regulation of puberty [7]. There is evidence that leptin, a 16 kDa hormone product of the *Ob* gene, synthesized by adipocytes, plays a permissive role [8, 9].

Although the lower limit of normal for the onset of puberty is contestable, the average age for this process is generally accepted to be 9–10 years for girls and 10–11 years for boys [2, 10]. Delayed puberty can be defined as failure to demonstrate signs of pubertal maturation by an age that is  $\geq 2$  standard deviations above the population mean [2]. Lack of testicular enlargement by age 14 in males, lack of breast development by age 13 in females, absence of menarche by age 16 in girls, or absence of menarche within 5 years of pubertal onset [11, 12] is defined as, delayed

puberty. Interestingly, males present far more often for evaluation of delayed puberty, but it has been suggested that this is in part due to a referral bias [1, 13].

## Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism (HH) is the commonest of the groups in both sexes and includes many pathologic disorders that can be further subdivided into constitutional delay of growth and puberty (CDGP), functional hypogonadotropic hypogonadism (FHH), and permanent hypogonadotropic hypogonadism (PHH). This classification can facilitate the diagnostic process by appropriately directing early evaluation efforts. HH is defined as lack of normal gonadal function secondary to low or absent gonadotropin function. In this case, the problem can be in the

pituitary gland itself, or it can be related to hypothalamic dysfunction (delayed activation of the gonadotropin-releasing hormone (GnRH) pulse generator). In addition to low or absent LH/FSH, sex steroid concentrations will be in the prepubertal range and bone age is typically delayed. Concentrations of adrenal androgens may be normal. The delay in puberty can be either temporary or permanent. Isolated hypogonadotropic hypogonadism is diagnosed if endogenous puberty has not begun by the age of 18 years [2].

### **Constitutional Delay of Growth and Puberty**

CDGP is the most common cause of delayed puberty especially in males (65 % of boys and 30 % of girls with delayed puberty) [1]. It is a benign variant of normal growth and development and, is notably, a diagnosis of exclusion. Typically, a child will be of normal size at birth and in infancy. At some point in early childhood, a decrease in growth velocity (GV) causes a decline in height centile for age growth curve. Normal growth then resumes with the child growing at an age-appropriate GV and at a consistent but low height percentile for age. This represents a global delay in biologic maturity affecting puberty and bone maturation. Height is usually appropriate for genetic potential when plotted for bone age. There is also usually a family history of “late bloomers” in the family—history of delayed puberty in the patient’s parents or siblings (77 %) [14]. They exhibit a relatively normal prepubertal growth velocity and protracted prepubertal growth nadir. The discordance in height vs. peers is exacerbated by a relatively lower growth velocity compared to peers who are experiencing a pubertal growth spurt. The growth velocity and height, however, should remain normal for bone age and pubertal stage. After HPG axis maturation, secondary sexual characteristics appear in their natural sequence with normal secondary sexual characteristic development. In 93 % of cases spontaneous

pubertal maturation occurs by 18 years and has an excellent outcome. In some cases, the constitutional delay of puberty superimposed on constitutional short stature and final height may be shorter than genetic potential [15].

Diagnosis of this condition is ultimately a matter of watchful waiting with close monitoring of growth and development. However, judicious evaluation to rule out other conditions and to support the likelihood of CDGP is important. Clustering of CDGP has been clearly established [1, 14] and the pericentromeric region of chromosome 2 harbors a gene predisposing to pubertal delay [14]. Growth charts, if available, should be reviewed to demonstrate typical CDGP pattern. In CDGP, both adrenarche and gonadal enlargement occur later than average; whereas in isolated HH, there is dissociation of adrenarche and gonadarche, with adrenarche occurring at normal age [1, 16]. GV and serum somatomedin-c (IGF1) should be monitored and remain normal for pubertal status. Evaluation may reveal low/normal gonadotropins and a delayed bone age. However GnRH agonist stimulation testing is not helpful in differentiating CDGP and permanent HH [17]. A positive response to GnRH agonist is suggestive of CDGP. To date, no single lab test or hormone stimulation protocol has the sensitivity and specificity to make this diagnosis. Response to sex steroid replacement therapy, which will often trigger activation of the hypothalamic–pituitary–gonadal (HPG) axis in CDGP but not in permanent HH, may aid in the diagnosis. Baseline, morning testosterone concentration of  $\geq 20$  ng/dl suggests the appearance of pubertal signs within 12–15 months [18]. A very low basal serum follicle-stimulating hormone (FSH) [ $< 0.2$  IU/L by immunochemiluminometric assays (ICMA) and  $< 1.0$  U/L by immunofluorometric assays (IFMA)] is suspicious of HH [19, 20]. Serum inhibin B (INHB) measurement will help to discriminate HH from CDGP. INHB is produced by sertoli cells upon FSH stimulation and is a reflection of sertoli cell integrity [21]. A baseline INHB concentration of  $> 35$  pg/ml is highly suggestive of CDGP [21].

## Functional Hypogonadotropic Hypogonadism

FHH represents another form of temporary, reversible HH. It accounts for about 20 % of children with delayed puberty [1]. Within this category is a broad range of pathology that highlights the complexity of the HPG axis and the diverse factors that must coordinate to initiate puberty. The most common diagnoses are related to chronic or underlying illnesses, such as hypothyroidism, cystic fibrosis, Crohn's disease, inflammatory disorders that produce cytokines, immunosuppression seen in perinatally HIV-infected children, and chronic renal failure [1, 22, 23]. The mechanism of pubertal delay in the case of underlying illness is thought to be manifold, involving a combination of factors that include, but not limited to, undernutrition, stress, and medications such as corticosteroids resulting in abnormal gonadotropin secretion [22]. The implicated genetic variations are in genes that have been associated with idiopathic hypogonadotropic hypogonadism [24]. As aforementioned, a common cause of FHH is malnutrition, as seen in anorexia nervosa or intense exercise resulting in HPG dysfunction. The connection between weight, especially body fat mass and puberty, has been extensively studied [8, 25, 26].

A thorough and detailed history may reveal systemic complaints, eccentric eating habits, or an obsession with exercise and weight loss. Physical exam may be revealing at times: weight and BMI will typically be low for age, and erosion of dental enamel and callused knuckles may suggest eating disorders. Laboratory evaluation may demonstrate elevated sedimentation rate and/or other inflammatory markers. Further evaluation depends on the clinical situation, but thyroid function should be assessed in all cases of HH.

## Isolated Gonadotropin Deficiency

Isolated GnRH deficiency resulting in low or inappropriately normal gonadotropins and absent or incomplete puberty could be associated with

abnormalities in craniofacial, skeletal, neurologic, renal, and olfactory systems. X-linked gene, *KALI*, found in GnRH-deficient men causes isolated gonadotropin deficiency known as Kallman's syndrome (KS) [27, 28]. This condition is caused by abnormal migration of embryonic GnRH and olfactory neuronal cells to the hypothalamus, resulting in HH and anosmia or hyposmia. *FGFR1* mutations are autosomal and are often associated with cleft lip/cleft palate, syndactyly, or skeletal abnormalities. Other cases of permanent isolated HH have historically been referred to as idiopathic HH (IHH). More recently, several genetic mutations have been discovered in some of these cases. Rare sequence variants (RSVs) in genes involved in GnRH neuronal migration (*FGF8*, *FGFR1*, *KALI*, *PROK2*, *PROKR2*, and *NELF*), secretion (*GNRH1*, *GPR54*, *TAC3*, and *TACR3*), and receptivity (*GNRHR*) have been reported to contribute to GnRH deficiency in both men and women [28, 29]. Most notably GnRH receptor mutations causing GnRH insensitivity and G-protein-coupled receptor 54 mutations causing impaired gonadotropin secretion have been identified [27]. At the time of puberty, the affected patients may have adrenarche—some pubic hair may be there, but little or no breast development or axillary hair and present with primary amenorrhea. HH is reported in leptin deficiency, where puberty can be induced by recombinant leptin [9]. HH has also been reported in *DAX1* mutations. *DAX1* is a nuclear receptor protein encoded by the *NROB1* and associated with X-linked congenital adrenal hypoplasia and HH, resulting from defects in the production of gonadotropins by the pituitary.

In all cases of isolated HH, other pituitary hormones should be assessed to confirm that the defect is truly isolated to gonadotropin secretion. In KS there is often associated decreased olfaction, synkinesia (mirror movements), sensorineural deafness, unilateral renal agenesis, and pes cavus. Brain imaging in cases of KS may show aplasia/hypoplasia of olfactory bulb and sulci. Some patients with isolated HH will have a positive family history, but most cases are sporadic. Genetic testing for associated mutations is possi-

ble, but not sensitive for diagnosis as the majority of isolated HH is idiopathic that is not associated with identified genetic abnormalities [3]. It can be particularly challenging to differentiate between CD and isolated HH. A reversible form of congenital GnRH deficiency also has been identified where the activation of the GnRH–gonadotropin axis is markedly delayed and the affected subject undergoes a sustained reversal of hypogonadotropism by age 18 [30]. Definitive diagnosis of GnRH deficiency cannot be made before 18 years.

### Multiple Pituitary Hormone Deficiencies

Hypogonadotropic hypogonadism as part of a constellation of multiple pituitary hormone deficiencies (MPHDs) can occur in the setting of central nervous system (CNS) tumors (i.e., craniopharyngioma, germinoma, hypothalamic glioma, prolactinoma), non-tumoral lesions (i.e., histiocytosis, granuloma, hydrocephalus, vascular lesions), cerebral dysgenesis, CNS trauma or infection, and destructive medical therapies such as radiation therapy. Genetic mutations, including defects in transcription factors such as PROP1, HESX1, LHX3, and LHX4, have also been identified in these cases [27].

Craniopharyngiomas are the predominant cause of permanent HH in children [1]. They are benign tumors that arise in the suprasellar region of the brain and may cause symptoms related to increased intracranial pressure and/or pituitary gland and optic nerve dysfunction. Growth hormone deficiency is the most common endocrinologic disorder, but all pituitary hormones can be affected and most adolescents presenting with these tumors will have delay in puberty [31]. Surgery and radiation therapy may further damage pituitary and hypothalamic function leading to permanent hormone deficiencies. Depending on dose and anatomical location, intracranial radiation therapy, in particular, causes irreversible damage to the hypothalamic–pituitary axis. It usually affects the hypothalamus to a greater extent than the pituitary gland and precocious puberty is more common than delayed puberty [32].

Septo-optic dysplasia (SOD) with midline cerebral dysgenesis can cause pubertal delay. It is characterized by congenital absence of the septum pellucidum, bilateral optic nerve hypoplasia, and hypopituitarism. There is significant variability in the severity of affected children, but typically involves visual impairment and pituitary hormone deficiency with radiologic abnormalities of the septum pellucidum or corpus callosum. It is occasionally associated with HESX1 gene mutations [33].

In any case of MPHD, laboratory assessment of thyroid function, adrenal function, growth, and electrolyte balance is indicated. Physical exam should include a thorough neurologic examination. A careful history should include review of past or recent head trauma, CNS infection, or intracranial radiation therapy. A review of systems should be performed with particular attention to visual change, headache, vomiting, fever, polyuria, polydipsia, poor growth, and salt craving. In most cases of MPHD, brain and pituitary imaging is a requisite and, if SOD is considered, an ophthalmologic exam is indicated to evaluate optic nerves and vision. Genetic testing is not indicated in all patients, but for those with a family history of MPHD and specific radiographic findings, targeted testing for specific mutations may be indicated [34].

### Genetic Syndromes

There are several congenital syndromes that have HH as one of the primary findings. The most well-known syndrome is Prader–Willi syndrome (PWS). It is caused by loss of imprinted genetic material from the paternally derived chromosome 15. In addition to HH, it is marked by neonatal hypotonia, feeding problems in infancy, obesity, hyperphagia, developmental delay, small hands/feet, and short stature. It is usually sporadic.

CHARGE syndrome is another common syndromic cause of HH [1]. This acronym stands for coloboma, heart defects, choanal atresia, retarded growth and development, genital hypoplasia, ear abnormalities, and/or hearing loss. Mutations in the CHD7 gene have recently been identified in around 2/3 of affected patients [35] and it has

been suggested that the developmental abnormality causing HH in this condition may be similar to that seen in KS [36]. It is an autosomal dominant mutation but most cases are sporadic. Bardet–Biedl syndrome also includes HH as a primary feature. Other manifestations of this rare, autosomal recessive condition include rod-cone dystrophy, obesity, renal dysfunction, developmental delay, and postaxial polydactyly.

The presence of other dysmorphic characteristics associated with a syndrome in addition to HH warrants further evaluation, e.g., for PWS, genetic testing, preferably with DNA-based methylation testing [37]. CHARGE and Bardet–Biedl syndromes are both diagnosed clinically. CHARGE syndrome diagnosis is based on major and minor criteria, but genetic testing for CHD7 mutation is available. Similarly, there is genetic testing for 14 associated genetic mutations for Bardet–Biedl, but the diagnosis is based on the presence of primary and secondary phenotypic features [38].

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## Hypergonadotropic Hypogonadism

Hypergonadotropic hypogonadism (HHG) causes delayed puberty due to primary gonadal failure. By definition, these disorders have elevated levels of gonadotropins without concomitant increase in sex steroid concentrations and without signs of pubertal maturation. Within this category lie primarily disorders of gonadal dysgenesis and gonadal injury.

## Gonadal Dysgenesis

Gonadal dysgenesis is the most common cause of HHG in children [1]. It is usually related to chromosomal abnormalities and hence chromosomal analysis is fundamental in the evaluation of children with HHG. In females, Turner's syndrome (TS) is a condition of X-monosomy (45, X) or structural abnormalities of an X chromosome. Mosaicism is common (50 % may have 45X/ mosaic karyotype). Girls have short stature and lack of normal pubertal development caused by

streak ovaries and premature ovarian failure. The degree of pubertal maturation is variable with occasional spontaneous menarche and rare fertility [39]. Other characteristics include heart and renal abnormalities, webbed neck, and broad chest. Mixed gonadal dysgenesis (MGD) can also occur similarly with X-monosomy/XY mosaicism. This protean genetic disorder can range in phenotypic presentation depending on the degree of mosaicism, from phenotypic female to phenotypic male.

Klinefelter's syndrome is a chromosomal abnormality found in males presenting with delayed puberty. In this case the underlying karyotype is 46-XXY. Along with HHG, this condition is characterized by tall stature, gynecomastia, decreased upper to lower segment body ratio, and learning disabilities. Other less prevalent disorders of gonadal dysgenesis in 46XY karyotype are Swyer syndrome (46XY, streak gonads), Drash syndrome, Frasier syndrome, mutations of SOX-9, DAX 1 with duplication of Xp21, and mutations in the SF 1 [12]. Additionally, certain disorders of sex development can present as HHG. For example, children with AIS or 5-alpha reductase deficiency (5-ARD) are genetically XY but are often raised in female because of ambiguous or female external genitalia. They may present with pubertal delay or primary amenorrhea when there is a failure to progress through normal female puberty.

Rare cases of gonadotropin receptor mutations (LH/FSH receptor mutation in XX females) with normal breast development, primary or secondary amenorrhea, elevated serum LH/FSH [depending on mutation of LH/FSH receptor], low estradiol level, and infertility have been reported. LH receptor mutation (homozygous or compound heterozygous inactivating mutations of the LH receptor) in XY males presents with male pseudohermaphroditism—female external genitalia/micropenis, absence of Mullerian structures, Leydig cell hypoplasia, lack of breast development, and HHG [11, 40, 41].

FSH  $\beta$  subunit gene mutation presents with delayed puberty, primary amenorrhea, elevated LH, and low or undetectable FSH [42, 43]. FSH receptor mutation presents with primary gonadal failure and HHG in females [42]. FSH is required



for follicular development and ovarian androgen and estrogen synthesis in females. Males present with oligospermia, but are fertile as FSH is not necessary for spermatogenesis [43].

## Gonadal Injury or Loss

HHG also occurs in children who have suffered gonadal damage, frequently as a result of treatment for an underlying malignancy. Gonadal tissue is particularly sensitive to radiation damage, but can also be affected by many chemotherapeutic agents [1]. Testicular tissue is more sensitive to damage by these cytotoxic therapies compared to ovarian tissue, and in all cases the risk is agent and dose dependent [44].

Gonadal tissue can also be injured by a wide spectrum of other processes, including trauma, infarction, and infection. In addition, certain disease processes can affect gonadal tissue and lead to pubertal dysfunction and infertility. Autoimmune polyendocrine syndrome type 1 (APS 1), for example, is associated with autoimmune-induced damage to gonadal tissue. Gonadal failure is much more common in females with this disorder and there is correlation between SCC autoantibodies and ovarian failure in women with APS 1 [45]. Galactosemia is also associated with HHG in female patients, especially those for whom treatment was delayed. It is thought that this is caused by cellular galactose toxicity occurring very early in life [46].

Complete loss of gonadal tissue can also present with delayed puberty. There are several indications for gonadectomy in the prevention and treatment of malignancy, including mixed gonadal dysgenesis and selective cases of androgen insensitivity syndrome (AIS) [47]. Additionally, anorchia is a male condition in which testes form normally in utero, as evidenced by normal male genitalia, but are absent at the time of birth, indicating loss sometime after the 14th-week gestational age. Cause is unknown. "Resistant ovary syndrome" is a condition due to abnormalities in gonadotropin receptors or antibodies to these receptors seen in 46 XX karyotypes, typically presenting with sexual immaturity

and primary amenorrhea, small ovaries with primordial follicles despite elevated gonadotropin concentrations [48, 49].

## Evaluation of Hypergonadotropic Hypogonadism

A careful history should disclose past surgeries, exposure to chemotherapy (especially of alkylating agents) or radiation, gonadal trauma or testicular torsion, prior episodes of orchitis, and the presence of other medical problems, including sickle cell disease, galactosemia, and autoimmune illnesses (especially hypoparathyroidism and Addison's disease). If autoimmunity is suspected, certain autoantibodies associated with APS1 can be measured with those against 21-hydroxylase being the most common. If an undiagnosed underlying process is suspected based on history or physical examination, further evaluation should be tailored specifically as needed. Ultrasound examination of abdominal gonads and/or chromosomal analysis is often warranted.

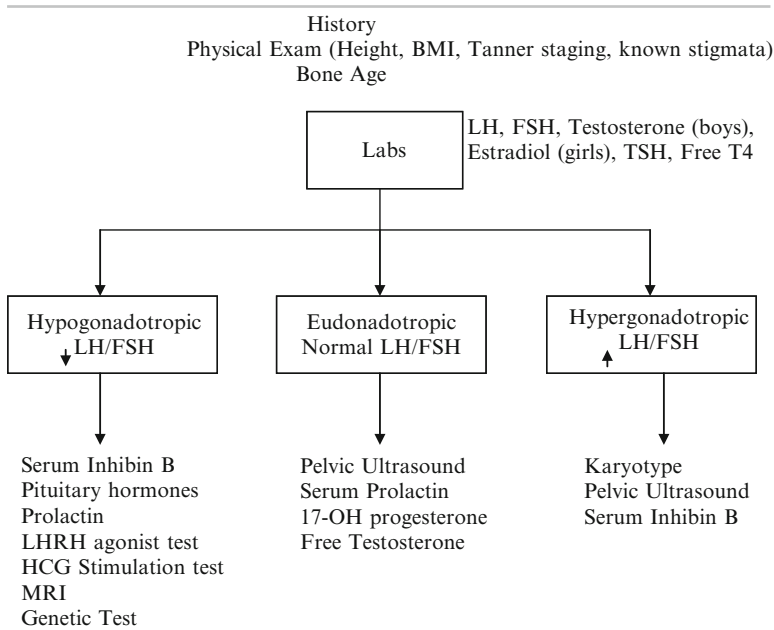
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## Eugonadotropic Hypogonadism

There are several conditions that can present with normal, pubertal gonadotropin levels with delayed or abnormal pubertal progression. Hormonal imbalances, for example, can cause failure to mature appropriately despite normal gonadotropin levels. Females with polycystic ovarian syndrome (PCOS) can undergo puberty appropriately but fail to proceed to menarche. These girls, usually obese, have normal reproductive anatomy and secondary sex characteristics, but may have signs of hyperandrogenism including severe acne or hirsutism. Hyperprolactinemia can also present with hypogonadism. Males will often have gynecomastia and females can have galactorrhea. The most common cause of elevated prolactin levels is prolactinoma.

Anatomic abnormalities are another cause of delayed puberty. Vaginal outflow obstruction, with imperforate hymen being the most common variant, can prevent menstrual outflow so

**Table 17.2** Diagnostic evaluation of delayed puberty



that a female has pseudo primary amenorrhea. Mullerian duct anomalies (MDA) are another type of anatomic abnormality that can present with primary amenorrhea. MDAs are classified according to the level and degree of malformation. Class 1 represents segmental or complete agenesis or hypoplasia that can involve any combination of the vagina, cervix, fundus, and fallopian tubes and is referred to as Mullerian aplasia [50]. Rokitansky–Kuster–Hauser syndrome is associated with uterine and vaginal hypoplasia/aplasia, where ovaries and fallopian tubes are preserved [12].

Evaluation of EH begins with a careful physical examination including assessment of weight, acanthosis, hirsutism, acne, gynecomastia or galactorrhea, neurologic or visual abnormalities, secondary sex characteristics, and external genitalia. Laboratory tests should include a serum prolactin. If PCOS is suspected, an elevated free testosterone level can strengthen the diagnosis and a 17-OHP level should be obtained to rule out nonclassical congenital adrenal hyperplasia. Chromosomal analysis is

warranted if a disorder of sex development is entertained. If serum prolactin level is elevated, an MRI of the brain/pituitary will help to confirm a prolactinoma. Abdominal and pelvic ultrasound is often helpful in EH cases and can identify polycystic ovaries, vaginal obstruction, and the presence of gonads and other internal reproductive organs.

**Diagnostic Tests**

Table 17.2 summarizes the diagnostic evaluation. A detailed history (especially of parental consanguinity, age of puberty and history of infertility in family members, anosmia, nutritional history, systemic illness), thorough physical examination (special attention to stature, BMI, accurate sexual maturity staging/Tanner staging, stigmata of known conditions and systemic illnesses, galactorrhea, etc.), bone age evaluation, and appropriate laboratory evaluations as indicated (i.e., karyotype, LH, FSH, estradiol/testosterone, other pituitary hormones, thyroid function, and

prolactin) will be a reasonable starting point. The aim of initial evaluation is to rule out underlying disorders causing delayed puberty. The assay methodology of serum LH and FSH determination is important as values obtained by ICMA are less than half of those obtained by IFMA [51]. Serum LH is a more specific marker of pubertal onset than FSH, whereas FSH is a more specific marker of primary gonadal failure [51]. Basal levels of LH and FSH help to differentiate between hypo/eugonadotropic vs. hypergonadotropic causes.

A delay in bone age is commonly seen in delayed puberty. If the bone age is >2 years delayed, the height prediction by Bayley–Pinneau tables overestimates predicted target height in CDGP [2, 51]. Karyotype is indicated in HHG. Pelvic ultrasound (US) in girls will help to delineate the presence or the absence of uterus and ovaries as well as any evidence of stimulation. Brain imaging is also indicated, especially in cases of hypogonadotropic hypogonadism. Serum INHB will help to assess the functional integrity of the sertoli cells. Depending on the clinical and laboratory assessment, imaging of brain and pelvic ultrasound is indicated. If basal gonadotropin levels are inconclusive, stimulation tests may be helpful in differentiating CDGP from HH. However, no single test has 100 % specificity/sensitivity.

*Role of stimulation tests:* If basal gonadotropin levels are inconclusive, stimulation tests may be helpful in differentiating CDGP from hypogonadotropic hypogonadism. However, no single test has 100 % specificity/sensitivity.

1. *GnRH or a GnRH agonist stimulation test:*

The gold standard for biochemical evaluation of HPG axis activation is determined by the LH response to a classical GnRH stimulation test. LHRH agonist stimulation test is more popular due to wide availability and also considered to be more discriminative than provocative LHRH test by some [52]. There is significant overlap in LH and FSH responses between CDGP and HH patients. Persistence

of low basal or GnRH agonist-stimulated LH and FSH in a late teen with a bone age >12 years may be suggestive of defective gonadotropin secretion. A positive response (i.e., predominant LH response over FSH response or peak LH >5 IU/L by ICMA and >8 by IFMA) will point towards the onset of central puberty and thus CDGP. In case of primary ovarian failure where the gonadotropin levels are only mildly elevated, GnRH agonist stimulation will reveal partial gonadal failure.

A variety of protocols exist, but an often used one is summarized below: leuprolide acetate injection 20 mcg/kg (maximum 500 mcg) administered subcutaneously. Draw blood levels FSH, LH, and estradiol/testosterone. Some institutions use blood draws at 0 h, 30 min, and 60 min. At our institution, blood is sampled at 0, 4, and 24 h. If the HPG axis is activated, there will be a two- to threefold rise in FSH and LH with maximal pituitary response of LH >5 IU/L at 4 h and maximal gonadal response of estradiol (E2) of >150 pmol/L (>40.86 pg/ml) and testosterone >3.15 nmol/L (>90 ng/dl) [53–55].

2. *Human chorionic gonadotropin (hCG) stimulation test:* There are many different protocols for this test [56–60]. The protocol commonly used in our institution is below: The hCG is administered intramuscularly at a dose of 3,000 IU/m<sup>2</sup> once a day for 3 days. LH, FSH, testosterone at baseline, as well as blood sampling for testosterone 24 h after the third injection needs to be drawn. An absolute serum testosterone concentration on day 4 of  $\geq 150$  ng/dl is normal and  $\leq 50$  ng/dl is diagnostic of HH.
3. *Growth hormone stimulation testing:* In subjects with short stature, delayed puberty, poor growth velocity, and delayed bone age, evaluation of serum IGF1 and provocative growth hormone testing will be helpful to rule out growth hormone deficiency. If there is significant short stature to warrant provocative growth hormone testing, sex steroid priming with estrogen/testosterone is necessary as this

may help to ameliorate the physiologic low growth hormone secretion associated with low estrogen levels [2].

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## Present and Future Therapies

Inadequate gonadal steroid secretion is the fundamental basis of delayed puberty.

Therapeutic goals are to develop secondary sex characteristics, to amass and sustain normal bone development, to maximize final height, and to restore fertility. Treatment of delayed puberty is variable and depends on diagnosis.

*Observation:* Most cases of temporary hypogonadism and EH do not require hormonal treatment to induce puberty. With GDGP, observation and “watchful waiting” are generally adequate, but short-term hormone therapy to “jump-start” puberty is sometimes indicated to prevent significant psychological distress, initiate a growth spurt, and/or activate the HPG axis.

In functional HH related to exercise, eating disorder, or chronic illness, the treatment is to improve overall health and nutrition. In regard to disorders of sex development, there is significant controversy surrounding the appropriate time for cosmetic surgery, gonadectomy, and HRT—current recommendations are complex and beyond the scope of this review [47].

*Hormone replacement therapy (HRT):* Permanent HH and HHG generally require sex steroid HRT to induce puberty and maintain physiologic hormone levels. Replacement of other pituitary hormones is also frequently required, especially in the case of *MPHD*. When using HRT to induce puberty there are several important considerations. Initiation of therapy must be timed appropriately to balance the benefits of developing according to population and physiologic norms with risk of premature epiphyseal closure and attenuated final adult height. Studies on boys with CDGP and girls with TS have both shown that initiation of hormone therapy at very low doses after around 14 years of age in boys or 12 years in girls has no significant negative effect on final adult

height while simultaneously promoting a natural emergence in the development of secondary sex characteristics [61–64]. In girls with any type of hypogonadism, HRT is the best treatment option as this will result in adequate development of secondary sex characteristics as well as that of uterus.

*Estrogen therapy* to induce female puberty is typically initiated with transdermal preparations of 17 $\beta$ -estradiol because of the very low dose of hormone replacement that is required. Typically treatment starts with using half of the lowest dose patch with 3.1–6.2  $\mu\text{g}/\text{daily}$  (1/8th–1/4th of the 25  $\mu\text{g}$  patch) and increased gradually by 3.1–6.2  $\mu\text{g}/\text{daily}$  every 6 months [2] over the next 2 years to an adult dose of 100–200  $\mu\text{g}/\text{daily}$  to mimic physiologic levels seen in puberty. Estradiol (E2) levels can be monitored to ensure appropriate dosing. HRT that is provided too rapidly, on the other hand, tends to promote unnatural development, including breast growth that occurs disproportionately in the nipple and areola [65]. Once full E2 dosing is reached and breast maturation is almost complete, cyclic oral progesterone at normal adult dose is added every 1–3 months to induce menstruation, necessary to decrease the risk of uterine cancer. Once menstruation has been established, contraception preparations can be used for HRT depending on patient preference [66]. In cases of HH in which permanent hypogonadism has not been confirmed, brief trials of HRT can be attempted once regular cycles occur in order to assess for activation of the HPG axis. If transdermal preparations are unavailable, HRT may be initiated with conjugated estrogens (Premarin<sup>®</sup>) 0.1625 mg daily, increased every 3–6 months to 0.325 mg daily, or ethinyl estradiol 2  $\mu\text{g}/\text{daily}$ , increased every 3–6 months up to 10  $\mu\text{g}/\text{daily}$ .

Initial therapy is with estrogen alone to maximize breast growth and to induce uterine and endometrial proliferation. Adding a progestin prematurely or administering combinations of estrogens and progestins early on may reduce ultimate breast size. Progestin is added to mimic the normal menstrual cycle after breast growth ceases (when full contour breast growth plateaus) or menses occur. Once menstruation is established with cyclic hormone treatment, discontinue intermittently for 1–3-month periods to determine if spontaneous menstruation occurs (in girls

with CD and FHH). In permanent hypogonadism: OCP is continued till the average age of menopause, ~50 years.

*Testosterone therapy* to initiate male puberty is generally started at 50 mg of depot testosterone as intramuscular injection once monthly for 3–6 months [2]. This will result in pubertal activation in CDGP [30]. If testes do not reach 4 ml in 1 year of treatment, it is highly likely that the patient will not develop puberty spontaneously (most likely, not CGDP). In that scenario, treatment may be discontinued for 3 months and HPG axis activation may be reevaluated. Subsequently, testosterone is increased to 100 mg per month with 25–50 mg increment in dose for approximately 18 months to complete the growth spurt (dosing should increase gradually to mimic physiologic puberty and prevent accelerated bone maturation). After growth is complete, further increase in dose can be made to 100 mg twice monthly. Testosterone levels and, in the case of HHG, LH levels should be monitored and used to adjust dose up to a maximum adult dose of 200 mg/twice monthly as needed to achieve serum concentrations in the normal range. Thereafter, increase testosterone dose to 250 mg, every 3–4 weeks. It has to be kept in mind that HRT in males only results in virilization without testicular development. Oral testosterone preparations provide less consistent serum testosterone levels and there is a risk for hepatic damage or carcinogenesis. Testosterone gels, frequently used in adults, are not well studied in children.

*Pulsatile GnRH or gonadotropin therapy:* Patients with permanent hypogonadism can occasionally achieve fertility through treatment with gonadotropin- or GnRH-based therapies and should be referred to reproductive endocrinology as needed. When fertility is desired treat with either exogenous gonadotropins or pulsatile GnRH. Pulsatile administration of exogenous GnRH is an effective therapy for stimulation of endogenous gonadotropin secretion, follicular development, and ovulation in women with GnRH deficiency. Mutations in the GPR54 (encoding the kisspeptin receptor, also known as KISS1R) reportedly can be corrected by the administration of GnRH [6, 27]. In

male hypogonadotropic hypogonadism, GnRH treatment will promote a physiological puberty with testicular development, virilization, and spermatogenesis. When spermatogenesis is achieved, subcutaneous hCG injections once or twice a week will maintain this development [11].

hCG has been used to treat subjects with permanent HH. A typical starting dose is 500 IU subcutaneously on Mondays, Wednesdays, and Fridays. Dilute the 10,000 U vial of powder with 5 mL of diluent for a 2,000 U/mL concentration. Obtain serum testosterone measurement in 1 month on a Monday prior to an injection. If the testosterone is <200 ng/dL, increase the dose to 1,000 U subcutaneously, up to a maximum dose of 1,500 IU (on M–W–F) and repeat a “trough” testosterone in another month. The hCG treatment will result in testicular enlargement, testosterone production, sertoli cell maturation, and spermatogenesis and thus offers better chances of future fertility.

Other treatment options such as combination of hMG/hCG or recombinant FSH/hCG [11] that are used in the management of hypogonadotropic males for fertility are beyond the scope of this chapter.

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## Future Therapies

Although current treatment of delayed puberty centers revolves around replacement of sex steroid hormones, advances in the identification of genetic mutations that underlie HH promise to increase our understanding of the physiology behind pubertal initiation [67]. This information could result in the development of improved targeted therapies and allow for normal pubertal progression. A potential future therapeutic agent for treatment of delayed puberty is agonists of kisspeptin peptides. In boys with CDGP and short stature, a potential therapeutic approach is aromatase inhibition, which may help to increase the final adult height [2, 68]. The treatments targeted to preserve future fertility such as cryopreservation of ovarian fragments prior to anticipated ovarian failure secondary to gonadotoxic treatment [69] and pulsatile hCG treatment for HH are beyond the scope of this chapter.

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Elizabeth Fudge

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### Hypothalamic–Pituitary–Gonadal Axis

At the onset of puberty, the hypothalamus increases gonadotropin-releasing hormone (GnRH) secretion which stimulates the anterior pituitary to produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH enter the systemic circulation and increase sex steroid production by the ovaries and testes. The primary sex steroid produced by the ovary is estradiol which promotes breast and reproductive system maturation in females. Estradiol, along with the inhibin and follistatin molecules produced by the ovary (follistatin is produced in other tissues as well), has a negative feedback effect on hypothalamic GnRH and pituitary gonadotropin release. In the testis, LH stimulates production of testosterone (and estradiol to a lesser extent) from Leydig cells, while FSH stimulates Sertoli cells to produce the inhibin peptides, and to mature into cells capable of supporting spermatozoa through the stages of spermatogenesis. Testosterone is responsible for growth of sexual hair, apocrine gland maturation, and increase in somatic (especially muscle) growth during puberty. Both testosterone and inhibins exert feedback inhibition

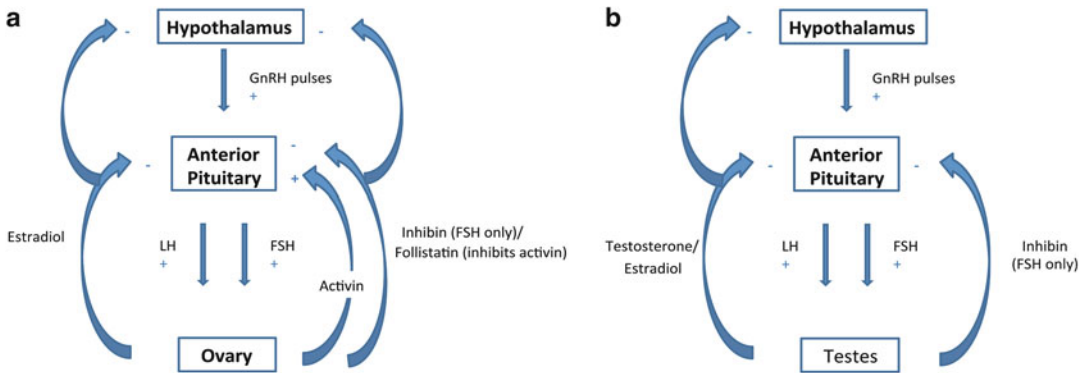
on the hypothalamic–pituitary–gonadal (HPG) axis in males [2, 3] (Fig. 18.1).

The HPG axis matures during fetal life, with gonadotropin release persisting into infancy. Peaks in gonadotropin and sex steroid levels occur between 6 and 8 weeks of life with levels comparable to those in early to mid puberty. Generally, peripheral effects of these sex steroids do not occur during this “mini puberty,” possibly due to the transient nature of the sex steroid increase. Gonadotropin levels reach a nadir at 6 months of life, although females may retain variable degrees of GnRH release during the first few years of life. The activation of HPG axis early in life is followed by a long period of quiescence through the prepubertal years when hypothalamic activity is suppressed. During the childhood years, the pituitary gland remains responsive to hypothalamic GnRH stimulation, with a characteristic response of greater FSH release than that of LH.

At the onset of puberty, the hypothalamus is reactivated, with enhanced, pulsatile GnRH secretion. Mean levels of FSH and LH increase, with a relatively greater rise in LH. Pubertal onset is initially manifested by LH pulses overnight. LH pulses increase in frequency and amplitude, and extend into the daytime hours as puberty progresses. The exact mechanisms that control hypothalamic GnRH activity and pubertal onset are incompletely understood, but are thought to reflect a balance between inhibitory and stimulatory neurotransmitters of the central nervous system [4–8].

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**Fig. 18.1** (a) Hypothalamic–pituitary–ovarian axis. (b) Hypothalamic–pituitary–testicular axis

## Normal Puberty

### Girls

The increase in sex steroids from the gonad, as well as adrenal androgens, is responsible for the physical changes of puberty. In girls, estradiol stimulates the onset and progression of breast maturity, genital growth (elongation of the vulva and growth of the labia minora), maturation of vaginal mucosa, uterine growth, and changes in body composition, mainly accumulation and localization of fat. Breast budding, or thelarche, is often the first sign of puberty in females. However, one-third of girls may experience pubic hair development, pubarche, before thelarche. Progression of breast development and pubic hair growth may be classified into Tanner stages (Fig. 18.2).

The adolescent growth spurt is seen early in puberty in girls, driven by the increase in estrogen, and the augmentation of growth hormone release by sex steroids. Menarche occurs approximately 2 years after the onset of puberty. Age at menarche correlates positively with skeletal maturity, and inversely with the remaining height potential. The average girl will gain an additional 4–6 cm after menarche. The duration of puberty is on average 3–4 years, although the tempo of puberty can vary as widely as 2–7 years between individuals.

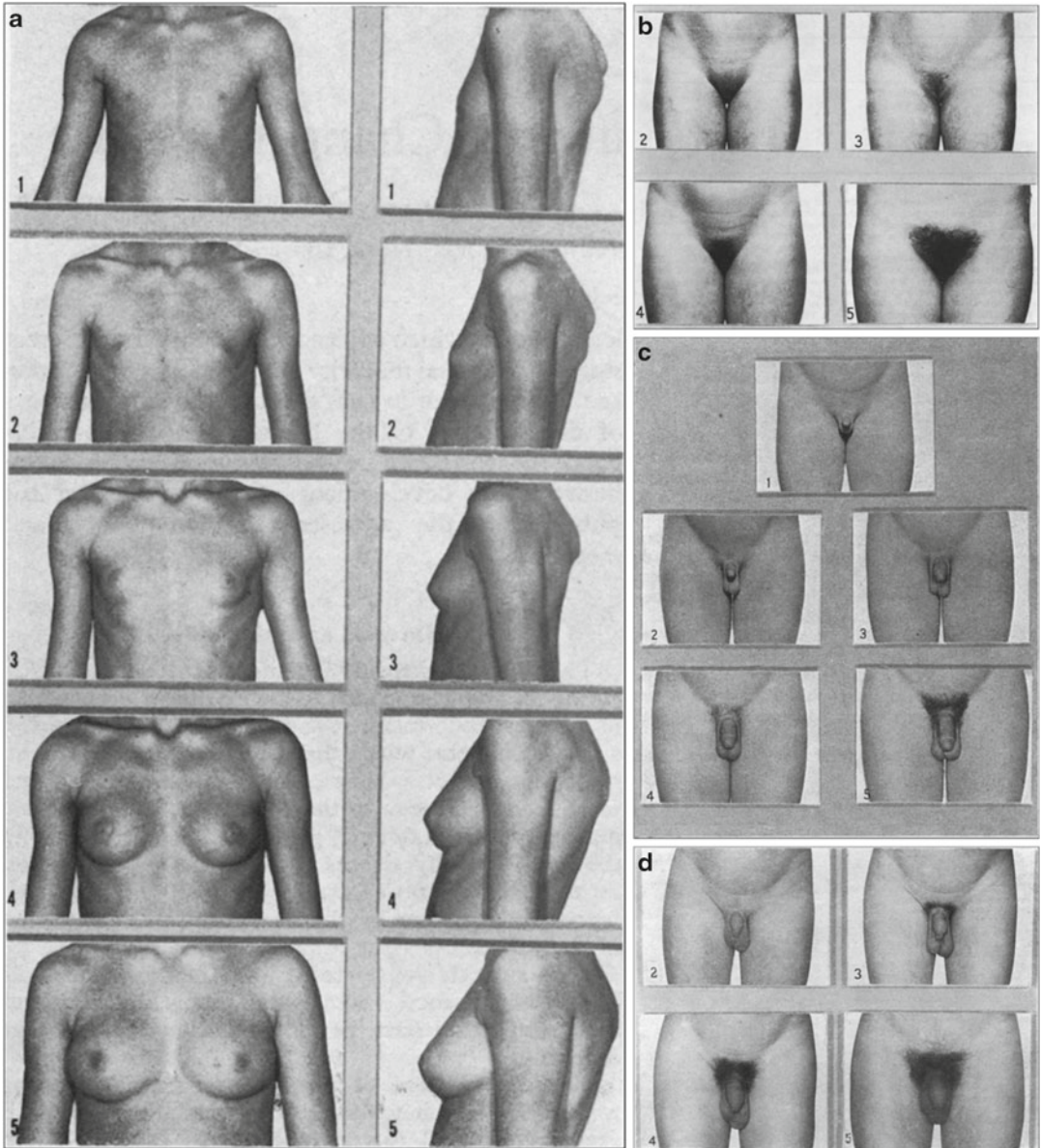
The historical ranges of normal pubertal timing were based on the data of Tanner and

Marshall from the 1960s. In these observational studies of primarily middle-class Caucasian children, 95 % of girls experienced breast development between ages 8.5 and 13 years, with an average age of 11.2 years. Black girls have been found to enter puberty earlier than girls of other ethnic groups, followed by Mexican-American girls, and then white girls [9, 10].

Other data on pubertal timing further support racial differences in the age of onset. These studies show that the early age limit and mean of Tanner 2 breast development for white girls is 8.0 and 10.4 years, for black girls is 6.6 and 9.5 years, and for Mexican-American girls is 6.8 and 9.8 years. The duration between pubertal onset to menarche was found to be approximately 2.3 years in these studies, with median age of menarche of 12.06 years in black girls, 12.25 years in Mexican-American girls, and 12.55 years in white girls [9–16].

### Boys

Testicular enlargement is the first sign of normal puberty in boys, with pubic hair growth often occurring around this time. A testicular volume  $\geq 3$  ml, or a longitudinal axis of  $\geq 2.2$  cm, is indicative of puberty. Axillary hair growth begins at mid-puberty, and hair growth in androgen-sensitive areas progresses. Male puberty can be classified according to Tanner stages of genital development and pubic hair (Fig. 18.2).



**Fig. 18.2** (a) Standards for breast ratings. (b) Standards for pubic hair ratings. (c) Standards for genital ratings. (d) Standards for pubic hair ratings (from Tanner 1969, [www.childgrowthfoundation.org](http://www.childgrowthfoundation.org))

Peak growth velocity in boys occurs in mid-puberty with increasing testosterone exposure. Males experience an increase in lean body mass, and a relative decline in body fat during this time. Estradiol levels increase during mid-puberty as the result of conversion of increasing levels of testosterone, potentiating growth and skeletal maturation. Spermarche, which is the onset of sperm production, occurs at an average age of 14 years [17].

The median age of development of Tanner stage 2 pubic hair is 11.2 years in black boys, 12.0 years in white boys, and 12.3 years in Mexican-American boys based on NHANES III data. In the earlier reports from Marshall and Tanner, 95 % of boys entered puberty between 9.5 and 13.5 years with an average of 11.6 years. The average duration of puberty in boys is 3 years [18–20].

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## Precocious Puberty

### Definition

Pubertal development at a younger age than expected for gender and population is considered precocious. The features include progression of pubertal signs, linear growth acceleration, and advancement of skeletal maturity. Classically, pubertal onset before age 8 in girls and age 9 in boys has been defined as precocious. However, racial differences in the timing of pubertal onset must be taken into consideration.

The lower age limit for defining precocious pubertal onset in girls has been controversial. Some experts suggest that the lower age cutoff should be 6 years for black girls and 7 years for white girls, with individuals older than these limits evaluated only if they meet certain criteria: significant skeletal advancement, predicted adult height < 2SD below genetic target, features suspicious of a central nervous system (CNS) lesion, rapid tempo of puberty, or psychosocial concerns. These recommendations have not been universally endorsed due to concerns that the lower age cutoff would fail to identify pathology in some individuals. For example, a retrospective review of patients referred for precocious puberty to a tertiary care center found that application of these lower age limits would have resulted in failure to identify treatable etiologies (such as congenital adrenal hyperplasia, pituitary adenoma, and neurofibromatosis) in 12 % of patients [21].

Until more data are available, careful evaluation of children with signs of secondary sexual development is warranted for girls younger than 8 years and boys less than 9 years. A comprehensive history and physical exam with clinical follow-up may be sufficient in those individuals between the lower and upper suggested age cutoffs whose evaluations indicate slow progression that does not raise concerns for underlying pathology [22].

### Normal Variants

When evaluating children referred for precocious puberty, normal variants must be considered. For instance, premature thelarche is isolated breast development in girls without other signs suggestive of true puberty. Premature thelarche often occurs within the first 2 years of life, with a second peak between ages 6 and 8 years. Breast development in these patients is minimally or non-progressive, and is not associated with linear growth acceleration or skeletal age advancement. In most cases, there is no underlying pathology, although some instances have been associated with the use of cosmetic or hair products containing lavender oil, tea tree oil, or placental extracts. Clinical follow-up is warranted in these individuals to monitor for pubertal progression as some may progress to true central precocious puberty [23–26].

### Premature Adrenarche

Adrenarche is the component of puberty that is not dependent on the HPG axis and may, therefore, vary in time of onset in relation to HPG activation. Adrenarche results when the adrenal cortex matures and increases production of androgens, including dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S), and androstenedione. Androgens are responsible for some of the physical changes of puberty such as acne, growth of sexual hair, and body odor from the development of apocrine glands. The appearance of these physical signs is referred to as pubarche. Adrenarche usually occurs just before or around the onset of puberty.

Adrenarche before the age of 8 years in females and 9 years in males is referred to as premature. The factors initiating premature adrenarche are not clearly understood. Children with benign premature adrenarche have features that are non- or slowly progressive. In addition, these children do not have growth acceleration, substantial bone age advancement, or other signs of true puberty such as breast development or testicular enlargement.

Levels of DHEA, DHEA-S, and androstenedione are often moderately elevated and consistent with Tanner stage of pubic hair. A small percentage of individuals with premature adrenarche may have a pathological cause such as central precocious puberty, nonclassical congenital adrenal hyperplasia, or androgen-producing tumor. Therefore, thorough clinical evaluation and follow-up are warranted in this group of patients. In addition, premature adrenarche has been associated with insulin resistance and polycystic ovarian syndrome later in life [27–31].

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## Differential Diagnosis

Precocious puberty may occur either by premature activation of the HPG axis which is termed central, or GnRH-dependent precocious puberty (GDPP), or by sex steroid exposure that is independent of hypothalamic–pituitary control, termed peripheral, or GnRH-independent precocious puberty (GIPP). The differential diagnosis is outlined in Table 18.1.

### Gonadotropin-Dependent Precocious Puberty

In GDPP, there is premature maturation of the HPG axis, with pubertal changes resulting from centrally mediated sex steroid production. The cause of the early onset of HPG activation may be congenital or acquired CNS abnormalities (e.g., hypothalamic hamartoma, astrocytoma, granulomatous disease, trauma). GDPP may also be idiopathic, which is estimated to occur 10–20 times more commonly in females compared to males. In addition, chronic exposure to sex steroids such as with untreated congenital adrenal hyperplasia may accelerate hypothalamic maturation and HPG activation resulting in GDPP.

In GDPP, the timing and sequence of pubertal events evolve in a normal pattern. The clinical signs are those of normal puberty including development of secondary sexual characteristics, linear growth acceleration, skeletal age advancement, and pubertal levels of sex steroids and gonadotropins.

### Gonadotropin-Independent Precocious Puberty

In GIPP, pubertal changes are induced by sex steroids from exogenous sources or from endogenous production that is not directed by hypothalamic GnRH secretion. Endogenous production of steroids may be derived from either gonadal or non-gonadal tissue. For example, precocious puberty may develop in individuals with elevated levels of adrenal androgens such as with congenital adrenal hyperplasia or adrenal tumors. Ovarian and testicular tumors secreting sex steroids may cause early pubertal development. In addition, tumors such as choriocarcinomas or hepatoblastomas can produce gonadotropins and cause GIPP. Gonadotropin receptors may be activated independently of gonadotropin activity, as in LH receptor-activating mutations. For instance, McCune–Albright syndrome (MAS) involves constitutive activation of G-protein-coupled receptors signaling through G<sub>s</sub> protein; the receptors for LH, FSH, TSH, GHRH, PTH, ACTH, and MSH function by this mechanism, and activation of these receptors can result in a variable number of endocrinopathies including precocious pubertal development. A more specific form of GIPP is seen in boys with dominantly transmitted sex-limited activation of the LH receptor at a young age. Rarely, long-standing untreated primary hypothyroidism may result in GIPP, thought to be due to chronically elevated TSH levels stimulating structurally similar LH receptors, known as the Van Wyk–Grumbach syndrome [32–35].

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## Key Points to the Diagnosis

### Which Children with Early Pubertal Development Should Be Evaluated?

In general, females less than 8 years and males less than 9 years with pubertal signs should be evaluated. Younger age heightens the concern for a pathological etiology, and warrants a more extensive evaluation. In those children who are approaching the lower age limit, a careful history,

**Table 18.1** Differential diagnosis of precocious puberty

Category	Presentation	Diagnosis	Treatment
GnRH dependent (central)			
Idiopathic	Pubertal changes in normal sequence, although may be more rapidly progressive Female:male >10:1	Pubertal gonadotropins and sex steroids, either basal or stimulated Skeletal age advanced	GnRH agonist
CNS abnormalities	Features of pubertal development similar to idiopathic	Similar to idiopathic	Therapy aimed at underlying lesion
Tumors	Clinical symptoms or signs of underlying CNS abnormality	Imaging (MRI or CT) showing CNS lesion in cases of tumor or structural abnormality	GnRH agonist in cases of hypothalamic hamartoma and some CNS lesions
Hypothalamic hamartomas			
Craniopharyngeomas			
Optic gliomas (may be associated with neurofibromatosis)			
Structural abnormalities			
Septo-optic dysplasia			
Hydrocephalus			
Arachnoid cysts			
Intracranial abscesses			
Other causes			
Granulomatous disease			
Infiltrative disease			
Trauma			
Surgery			
Radiation			
Chronic exposure to sex steroids with advanced maturation	Initial development out of sequence and/or progresses rapidly due to peripheral cause HPG activation results in onset of true puberty with features similar to idiopathic	Similar to idiopathic Laboratory findings consistent with underlying peripheral etiology (e.g., CAH)	Treatment of underlying disorder GnRH agonist required in most cases
GnRH independent (peripheral)			
General features	Isosexual or contrasexual pubertal changes which may progress rapidly and/or out of normal sequence		
Adrenal tumors	Virilization in girls, and precocious sexual development in boys	Elevated adrenal androgens such as DHEA, DHEA-S, androstenedione	Therapy directed at tumor including surgery and possibly chemotherapy
Adenoma	Gonads prepubertal	Other adrenocortical hormones such as cortisol may be elevated	
Carcinoma		Imaging revealing adrenal tumor	

Ovarian tumors Carcinoma Gonadoblastoma Granulosa cell Theca cell	Rapid pubertal progression in girls; feminization in boys	Elevated estradiol Prepubertal gonadotropins CT or ultrasound showing ovarian tumor	Tumor resection
Testicular tumors Leydig cell	Virilization in girls, and precocious sexual development in boys Asymmetrical testes in boys	Elevated testosterone Prepubertal gonadotropins CT or ultrasound showing testicular tumor	Tumor resection
Gonadotropin or hCG producing Choriocarcinoma Dysgerminoma Hepatoblastoma Teratoma	Pubertal development with testicular enlargement in males Rare in females; associated with isosexual pubertal development	Elevated LH, FSH, or $\beta$ -hCG Elevated sex steroids Evidence of tumor on imaging	Tumor resection Chemotherapy and radiation in some cases
Congenital adrenal hyperplasia	Premature pubarche and rapid growth Virilization in females Gonads prepubertal May lead to central precocious puberty	Elevated 17-OH progesterone and other adrenal precursors either basally or in response to ACTH stimulation	Glucocorticoid and mineralocorticoid replacement
Male-limited familial precocious puberty (testotoxicosis)	Occurs in males Virilization and rapid growth early in life Testicular enlargement	Pubertal testosterone levels Prepubertal gonadotropins	Ketoconazole Aromatase inhibitors Antiandrogens
McCune-Albright Syndrome	Isosexual development that occurs in unusual sequence Affects girls>boys Polyostotic fibrous dysplasia Café au lait lesions Other endocrinopathies	Pubertal sex steroid levels Pelvic ultrasound in females may show ovarian cysts GNAS1 mutation in samples from affected tissue	Tamoxifen Aromatase inhibitors GnRH $\alpha$ if central precocious puberty develops
Primary hypothyroidism	Isosexual pubertal changes associated with lack of expected growth acceleration Gonadal enlargement	Elevated TSH and low thyroxine level Gonadotropins prepubertal	Thyroid hormone replacement
Exogenous exposure to sex steroids	Various presentations depending upon substance	Variable; some compounds measurable in serum Gonadotropins prepubertal	Identify and remove exposure to compound

physical examination, and bone age determination may be sufficient if no other concerns arise during the initial evaluation.

### **Are the Pubertal Changes Progressive? If so, What Is the Sequence and Tempo of Changes?**

Precocious puberty is associated with progressive pubertal changes which can be differentiated from normal variants such as benign premature thelarche in which pubertal signs are non- or minimally progressive. Precocious puberty is associated with advancement of skeletal maturity and linear growth acceleration, features which are not seen in normal variants of development.

In GDPP, pubertal changes occur in a normal sequence with a tempo similar to normal puberty. On the other hand, children who have GIPP are more likely to have features of puberty outside of the normal sequence, and with aberrant timing. For example, a young boy with development of sexual hair and virilizing features without testicular enlargement is likely to have a peripheral source of androgen production such as an adrenal tumor. Furthermore, children who have a normal sequence of pubertal changes, but have rapid tempo of changes, are more likely to have GIPP. For instance, a young girl with breast development who progresses to menarche within 12 months is likely to have a peripheral source of estrogen production such as an ovarian tumor.

### **Are the Pubertal Signs Suggestive of the Source of Sex Steroids?**

Elevated estradiol levels will result in signs of puberty in girls, but will lead to feminization in males, with gynecomastia. Conversely, elevated androgen levels in females will lead to signs of virilization including hirsutism, acne, and clitoromegaly, but signs of puberty in males. Therefore, isolated virilization in females suggests a

peripheral etiology, and excludes GDPP. Feminization in males also excludes a central etiology, and most testicular etiologies with the exception of rare testicular tumors such as a feminizing Sertoli cell tumor.

### **Does the Patient Have Features of an Underlying Disorder?**

- Neurological signs such as changes in gait or vision, or symptoms of pituitary hormone deficiencies such as diabetes insipidus or growth hormone deficiency, raise suspicion for CNS abnormalities.
- MAS should be considered if there are café au lait spots, bone deformities on the face or long bones, or accelerated growth. In addition, patients with MAS often develop pubertal signs that are outside of the normal sequence. For example, menstrual bleeding often precedes breast development in girls with this disorder, and may occur as early as 4–6 months of age.
- Neurofibromatosis type 1 (NF1) may be associated with GDPP, usually but not exclusively in those with optic pathway gliomas. Primary features of NF1 are café au lait macules, axillary freckling, neurofibromas, optic nerve gliomas, and hamartomas of the iris (Lisch nodules).
- Signs of precocious puberty with absent linear growth are suggestive of primary hypothyroidism, although this is extremely rare with only approximately 12 reported cases in the literature [36].
- In patients with primary adrenal failure with precocious puberty, a DAX-1 (dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1) mutation should be considered. Rarely, patients with adrenal hypoplasia congenita (AHC) due to DAX-1 mutation may develop GDPP; these individuals may have primary adrenal failure during infancy. DAX-1 mutations may also be associated with Duchenne muscular dystrophy and glycerol kinase deficiency due to a contiguous gene deletion syndrome.



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## Evaluation

### Medical History

Pertinent history includes the age of onset of pubertal signs and their rate of progression, as well as timing of puberty in family members. Growth data are helpful to determine if there is growth acceleration. Symptoms of a CNS lesion such as headaches or seizures should be sought. Exposure to exogenous hormones should be explored; this may be from the cosmetic products noted above or contact with a parent's topical testosterone [37, 38].

### Physical Examination

Important anthropometric data include height, weight, and height velocity (if possible). A thorough neurological examination including visual fields and fundoscopic examination should be performed to evaluate for a CNS lesion. Careful examination of the skin may provide clues to the diagnosis; for example, café au lait macules suggest MAS or NF1.

Pubertal signs should be assessed to determine Tanner stage (previous figures). In girls, the diameter of glandular breast tissue and areola should be measured. Examination of the genitalia for signs of maturation may be helpful. In addition to the labial and vulvar changes noted above, an increase in clear mucous secretions and changes in vaginal mucosa from a thin, red mucosa to a thickened, pink-appearing mucosa are seen in girls with puberty.

In boys, testicular size and pubertal staging should be determined. Testicular volume  $\geq 3$  cc or longitudinal axis  $\geq 2.2$  cm suggests gonadotropin stimulation and likely GDPP. In a male with pubertal signs, but without testicular enlargement, a peripheral source of sex steroids should be sought. For instance, boys with constitutive activation of the LH receptor in the testis have relatively small testes for their degree of sexual maturation. If significant asymmetry of the testes is present, a testicular tumor such as a Leydig-cell tumor should be considered; some asymmetry, however, is common.

## Imaging Studies

A bone age film to determine skeletal maturity should be obtained in children with early pubertal development, recognizing the subjectivity and normal variation of this test. Significant skeletal advancement is present in GDPP, along with other signs such as growth acceleration and pubertal findings on physical examination. In individuals with signs of puberty which are progressive without bone age advancement, a peripheral source should be sought; more rapid increases in sex steroid levels can occur with GIPP compared to GDPP, and ossification of the growth centers lags behind sex hormone stimulation by some 6 months. In addition, those with normal variants of puberty such as premature adrenarche have skeletal age that is normal or slightly advanced, and pubertal signs that are nonprogressive.

Pelvic ultrasonography in girls to assess ovarian and uterine volumes can be useful in establishing whether an individual is pubertal, and for monitoring the progress of puberty. In cases of GIPP, abdominal-pelvic ultrasound should be performed to evaluate for an ovarian tumor or cyst. In addition, a testicular ultrasound study may be indicated in boys with GIPP to evaluate for a testicular mass [39].

Imaging of the CNS with magnetic resonance imaging (MRI) is indicated in most children with GDPP to evaluate for an intracranial lesion. There has been conflicting data about whether MRI should be performed in low-risk categories such as girls over the age of 6 years with GDPP. For example, one series reported no CNS abnormalities found in a group of females with the onset of GDPP after 6 years of age with estradiol levels  $<12$  pg/ml. However, another report found that 15% of girls in this age group had CNS lesions. A careful neurological examination, consideration of ethnicity, and estradiol levels can be used to determine whether an MRI of the brain is indicated in girls older than 6 years with GDPP. The vast majority of the brain lesions found in these girls are nonprogressive hamartomas that do not require surgical intervention. As idiopathic GDPP is less common in boys, an MRI of the brain is warranted in all males due to the higher likelihood of identifying intracranial pathology [40–42].

## Biochemical Studies

Initial laboratory assessment includes measurement of basal hormone levels including LH, FSH, and estradiol in girls, and testosterone in boys. Basal LH above 0.3 IU/L, estradiol level >20 pg/ml, and testosterone level > 50 ng/dl have been used to define GDPP, although these cutoffs depend upon the sensitivity of the individual assay. If basal hormone levels are consistent with puberty, then dynamic testing is not necessary [43].

As LH is pulsatile and initially elevated nocturnally in early puberty, a GnRH stimulation test may be needed to diagnose GDPP. To perform this test, a GnRH analog (GnRHa) is given with measurement of LH and FSH levels at baseline and 30–60 min after GnRHa is administered. LH response to GnRHa stimulation becomes more pronounced than that of FSH with pubertal maturation. A peak LH of 5–8  $\mu$ IU/ml is suggestive of GDPP, while lack of response is indicative of either prepuberty or GIPP. FSH response does not increase as dramatically as that of LH during pubertal development, and LH/FSH ratios may be helpful in determining pubertal status. An LH/FSH ratio less than 1.0 is considered prepubertal [44].

In patients suspected of having GIPP, biochemical evaluation for peripheral sources of sex steroids should be performed. Serum cortisol, DHEA, DHEA-S, and 17-hydroxyprogesterone should be measured in addition to the aforementioned tests. In boys, serum B-hCG can be measured for the possibility of a tumor-secreting hCG [45–47].

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## Present and Future Therapies

Treatment of precocious puberty depends upon whether or not the process is gonadotropin mediated. In GDPP, therapy is aimed at decreasing pulsatile GnRH release from the hypothalamus and, therefore, pituitary production of gonadotropins. In GIPP, treatment is directed at the underlying etiology of sex steroid production which may involve the gonads, adrenal glands, or exogenous sources.

## Treatment of Gonadotropin-Dependent Precocious Puberty

As noted previously, GDPP may be idiopathic in nature, or be associated with a CNS lesion. Children who have CNS lesions should undergo appropriate surgical, radiation, or chemotherapy as indicated. Hypothalamic hamartomas are generally not resected because there is significant morbidity from damage to the hypothalamus and pituitary function associated with surgical intervention. Hypothalamic hamartomas are typically monitored radiologically, and rarely cause neurological manifestations. Individuals with hypothalamic hamartomas may be treated with GnRHa therapy (discussed below) [48].

Precocious sexual development results in accelerated skeletal maturation and linear growth rate which may compromise adult height due to premature fusion of epiphyses. The extent of adult height potential that is lost depends upon the age of onset and rate of progression of pubertal changes. Younger age and more rapid progression of puberty result in greater loss of adult height. In addition, precocious puberty may be associated with psychosocial stress due to earlier development compared to peers; anxiety, withdrawal, and depression may occur in those with early puberty. The decision to treat a child with early pubertal development depends upon both the degree of compromise of adult height and psychosocial factors [49].

GnRHa therapy is the primary treatment for GDPP. GnRH agonists act by providing a tonic elevation of GnRH which occupies GnRH receptors on the pituitary gland, decreasing pituitary responsiveness to GnRH, thereby blunting pulsatile gonadotropin release. This continuous GnRH exposure restores the prepubertal state of the HPG axis. GnRHa is the only effective treatment for GDPP [50].

Patients being considered for GnRHa therapy should have pubertal basal or stimulated gonadotropin concentrations, progressive pubertal changes, linear growth acceleration, and advancement of skeletal maturity. Treatment should be considered for those with compromised adult height prediction (relative

to genetic height target) and those with significant psychosocial concerns from the parents or the child about further pubertal development.

Children with the onset of GDPP at a younger age will have early epiphyseal fusion and loss of adult height potential if not treated, and will have greatest benefit from therapy. Those children who are nearing the age of normal puberty at the time of diagnosis or who have slow progression of puberty are likely to have less benefit from GnRHa therapy, and may not require intervention. For instance, girls with GDPP who are started on GnRHa therapy before age 6 years have an average adult height gain of 9 to 10 cm, and those started on therapy between 6 and 8 years of age have average height gains of 4–7 cm. Although fewer data are available for boys, those starting on GnRHa therapy at an average age of 7.6 years had mean height gain of 6.2 cm. Height gains are likely to be less in those with more advanced bone ages. Because some children with precocious puberty may have slow progression of puberty, they may not require medical intervention with GnRHa to preserve height potential, especially in those nearing the age of normal puberty. Monitoring patients to assess the tempo of puberty before treatment is indicated in those who are not rapidly progressing or who are older [51–57].

### **GnRHa Dosing and Monitoring**

GnRHa are available as depot injections, short-acting injections, subcutaneous implants, and nasal spray, with the depot formulations and subcutaneous implants being the most commonly prescribed therapies. The depot formulation, leuprolide acetate, is available in either monthly or 3-monthly dosing which appear to be comparably effective in suppressing the HPG axis, although direct comparison in clinical trials is not available. The implantable form of GnRHa, histrelin, is also an effective therapy and may provide HPG suppression for up to 1 year [58–60].

The recommended dose of GnRHa therapy is sufficient to achieve pubertal suppression in most patients. Patients should be examined every 3–6 months, and skeletal maturity determined every 6–12 months. During the 1st 6 months of therapy, skeletal maturation may continue to accelerate at

the pretreatment rate as a result of ossification of pre-existing cartilaginous maturation. Adequacy of dosing may be determined by clinical and biochemical parameters. If HPG axis suppression is achieved, there will be lack of progression of pubertal signs such as breast development and testicular enlargement. Height velocity and rate of bone age advancement should decline.

In addition, levels of LH and estradiol (in girls) and testosterone (in boys) may provide evidence of HPG axis suppression. Two to three months after initiating therapy, LH and sex steroid levels may be obtained either just before the next dose, or at 30–60 min after therapeutic GnRHa dose is given. Prepubertal LH and sex steroid levels obtained before the next dose generally reflect HPG axis suppression. Normative data for LH levels post therapeutic dose may guide whether further investigation is necessary. For instance, one study found that an LH level of  $< 2.5 \mu\text{IU/ml}$  measured 90 min after GnRHa administration correlated with adequate pubertal suppression compared to GnRH stimulation testing. Biochemical parameters should be interpreted along with other clinical data, as LH and sex steroid levels are not well correlated with clinical response to GnRHa therapy. When pubertal suppression is not achieved, GnRHa dose should be increased with appropriate clinical follow-up to determine dose adequacy [61, 62].

The decision to discontinue GnRHa therapy must be individualized. In general, therapy is discontinued at an age when normal puberty would be occurring. Psychosocial factors including the child's preparedness for pubertal progression and menarche must be considered. Prolonged suppression of adolescent development can have a deleterious effect on accrual of peak bone mass. In some cases, therapy may be continued for a longer time if there are concerns about adult height potential, although height gains decrease with advancing age.

### **Safety**

Treatment with GnRHa appears to be safe and without significant long-term effects on the HPG axis. The HPG axis is reactivated within weeks to months after discontinuation of GnRHa therapy, with pubertal gonadotropin levels occurring within 6 months after cessation. Most girls

experience menarche within 18 months of discontinuing GnRHa, and small studies show normal testicular function in males after treatment. In addition, gonadal function in adulthood does not appear to be affected by GnRHa therapy [63].

Bone mineral density (BMD) may decrease for age during treatment with GnRHa due to suppression of sex steroids during a critical time of bone mineral accrual. Individuals with precocious puberty have greater than average BMD for age before therapy, and have little change in BMD during therapy, yielding a lower than average BMD at the end of the treatment. However, as puberty resumes after therapy is discontinued, the resulting increase in sex steroids normalizes BMD by mid-puberty. Due to these concerns, adequate intake of calcium and vitamin D is encouraged in patients receiving GnRHa therapy [64, 65].

Data on adult height gain from GnRHa therapy are variable due to the wide spectrum of ages and degrees of bone age advance when therapy is initiated. Factors associated with greater gains in adult height are earlier onset of puberty, younger age, less advanced skeletal age, longer duration of therapy, and initiation of therapy close to the onset of puberty. Growth rates and adult height after cessation of GnRHa therapy are often less than predicted based on skeletal maturity and height at the time treatment is discontinued [66–69].

### **Treatment of Gonadotropin-Independent Precocious Puberty**

GIPP treatment is directed at the underlying etiology, and does not respond to GnRHa therapy. For example, individuals with congenital adrenal hyperplasia (CAH) should be placed on corticosteroid replacement to decrease production of adrenal androgens leading to precocity and bone age advancement. Many children with CAH develop GDPP due to delayed diagnosis with long-term exposure to sex steroids, and require GnRHa therapy.

Children with tumors secreting sex steroids or gonadotropins should undergo appropriate surgical or medical treatment for those conditions.

Tumors of the gonads and adrenal gland are treated by surgery. Adjuvant chemotherapy may be necessary with some adrenal tumors depending upon surgical results, histology, and presence of metastases. Individuals with hCG-secreting tumors possibly require surgery, chemotherapy, and radiation depending upon the location and histological type of tumor.

In children who have premature development due to exogenous exposure to sex steroids, the exposure must be identified and removed. A careful history is critical in determining the exposure. Removal of the offending agent often results in regression of pubertal changes.

Precocious sexual development is the most common endocrine manifestation in MAS, which is far more common in girls than boys. Estrogen and testosterone are produced autonomously by the gonads, in girls and boys, respectively. Other endocrinopathies may include overproduction of thyroid hormone, growth hormone, and cortisol.

Treatment of GIPP in girls with MAS is targeted at inhibiting the aromatization of testosterone to estradiol, and at the blockade of estrogen receptors. Aromatase inhibitors (such as testolactone, letrozole, and anastrozole) reduce ovarian estrogen production, decrease menses, and slow the rate of skeletal maturation in MAS. Tamoxifen, an antiestrogen, may slow pubertal progression and skeletal maturation, as well as reduce the frequency of menses. Some patients with MAS develop GDPP, and may respond to GnRHa therapy. MAS in males is manifested as overproduction of testosterone, although males are rarely affected. The treatment of males with MAS is similar to that for male-limited precocious puberty (MLPP) outlined below [70–72].

MLPP, or familial testotoxicosis, is an autosomal dominant disorder characterized by GIPP in males due to autonomously functioning LH receptors. An activating mutation of the LH receptor in Leydig cells results in unregulated testosterone production and precocious puberty most commonly between the ages 1 and 4 years. As in MAS, treatment for MLPP is directed at inhibiting the production and blocking the action of sex steroids. Inhibitors of androgen biosynthesis such as ketoconazole are effective in reducing testosterone

levels, decreasing the growth velocity and the rate of skeletal age advancement. Ketoconazole therapy may also improve adult height, especially if started at an early age. Alternatively, combination therapy with antiandrogens and aromatase inhibitors such as spironolactone and anastrozole may be beneficial in reducing pubertal progression, slowing linear growth and skeletal maturation. These therapies appear to improve predicted adult height based on skeletal maturity, although data on adult height are lacking. Secondary GDPP may develop in individuals with MLPP necessitating treatment with GnRHa [73–80].

## Conclusions

In summary, the child presenting with precocious puberty may be classified into three categories: GDPP, GIPP, or a normal variant. A thorough evaluation is warranted for girls less than 8 years of age and boys less than 9 years of age or in those whose evaluation is concerning for underlying pathology. The goals of therapy in children with precocious puberty are to preserve adult height potential and alleviate psychosocial stress that may accompany early puberty. Treatment with GnRHa is safe and effective in individuals with GDPP, with greater height preservation in those of younger age who have less advanced skeletal ages, and on longer duration of therapy. Treatment should be aimed at the underlying etiology or the mechanism of the sex steroids in those with GIPP.

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Understanding the physiology of sexual differentiation is a prerequisite for the development of models for diagnosis and treatment.

In humans and in most mammals, the process of sex determination and differentiation are associated closely with the presence or absence of the Y-chromosome karyotype. The process is divided into three steps [1]:

1. Chromosomal sex determination (XY or XX), which is established at fertilization.
2. Determination of gonads to testes or ovaries.
3. Differentiation of internal and external genitalia male or female, from undifferentiated structures present in the embryo (dependent on the presence or absence of testicles).

The term “sex determination” refers to the molecular processes that lead the undifferentiated gonad to differentiate to testes or ovaries and occurs in the following sequence [1]:

- Development of undifferentiated gonads (bipotential) from the urogenital ridge.
- Migration of primordial germ cells during the fourth and fifth gestational week from the endoderm of the yolk sac dorsal, reaching the crest urogenital at about 6–8 weeks.
- Testicular differentiation and production of testosterone in the ninth gestational week.
- Ovarian differentiation with germ cell meiosis between the 11th and 12th gestational weeks.

In turn the expression “sexual differentiation” refers to the specific hormonal actions that lead to phenotypic sex of the individual and involves the development of internal genitals, the urogenital sinus, and the external genitalia.

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## Internal Genital Development

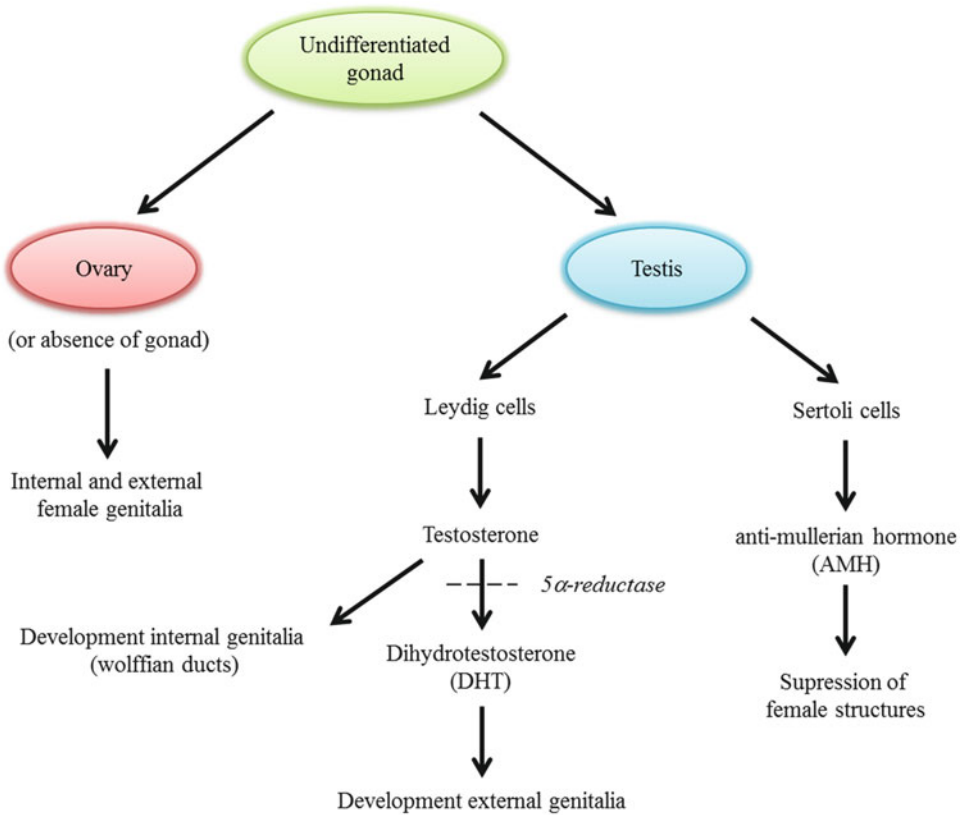
- By 7 weeks of pregnancy a fetus has a dual system—Wolffian ducts with the potential for the development of a male and Müllerian ducts with the potential for the development of a female.
- The Müllerian ducts regress in the presence of the testis while the Wolffian ducts develops in the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts.
- In the absence of testicles, the Wolffian ducts involute and the Müllerian ducts develop in the fallopian tubes, uterus, and upper third of the vagina [2].

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**Fig. 19.1** Hormonal control of sexual differentiation

## Urogenital Sinus Development

- Under the influence of androgens the urogenital sinus narrows to form the posterior urethra. The urogenital sinus forms the prostate gland and the Cowper's bulbourethral glands.
- In the absence of androgens the urogenital sinus differentiates in the lower two-thirds of the vagina and urethra, developing Skene's paraurethral glands and Bartholin's vestibular glands [2].

## External Genitalia Development

In contrast to the internal genital, external genitalia stems from a common anlage, a midline genital tubercle formed in the eighth gestational week

with urethral folds surrounded by side labioscrotal swellings.

- The genital tubercle develops to form the glans penis in males and the clitoris in females.
- The urethral folds develop forming the corpus spongiosum in males and the labia minora in females.
- Labioscrotal swellings fuse in the midline to form the scrotum and ventral penis in males and remain separated to form the labia majora in females [2].

## Hormonal Control of Sexual Differentiation (Fig. 19.1)

The fetus has an inherent tendency towards female differentiation. In the absence of gonads, the fetus will develop internal and external normal female genitalia. In contrast normal male

differentiation requires intact testis (with Leydig cells and Sertoli functioning) and the 5 $\alpha$ -reductase type 2 enzyme [3].

Male differentiation occurs as follows:

- Wolffian ducts development, under the influence of testosterone secreted by Leydig cells.
- Müllerian ducts regress, under the influence of a peptide produced by Sertoli cells, the anti-Müllerian hormone (AMH).
- Development of the urogenital sinus under the control of dihydrotestosterone (DHT), synthesized from testosterone in tissues containing the 5 $\alpha$ -reductase type 2 enzyme.

The following *keys points to diagnosis* should be considered:

- The testis has a paracrine effect on adjacent tissue so that a testicle results in the Wolffian development and Müllerian regression, while a typical gonad may be associated with Wolffian regression and Müllerian development. This situation can be found with mosaicism 45X/46XY (often called mixed gonadal dysgenesis).
- The presence of the uterus in a newborn with ambiguous genitalia indicates the presence of an ovary or the absence of gonadal tissue, or if there, testicular tissue should be dysgenetic with poor function of Sertoli cells.
- 46XY individuals with partial or complete androgen resistance secrete and respond normally to AMH, and no development occurs in the fallopian tubes, uterus, and upper third of the vagina.

## Genetic Control of Gonadal Determination and Sexual Differentiation

Gonadal determination results from interplay between the SRY gene and others genes (e.g., SOX9, SF1, WT1, GATA4). The AMH gene (19p chromosome) controls the secretion of AMH by Sertoli cells. AMH has paracrine action on the AMH type II receptor (12q). Both testosterone and DHT mediate their effects via the androgen receptor (AR) (Xq11-q12), which is a transcription factor. Testicular descent is mediated by the secretion of certain factors such as insulin-like 3 (INSL3) and the G-protein coupled receptor (GREAT) [3].

Figure 19.2 summarizes the main genes involved in gonadal determination and sexual differentiation.

Mutations or deletions in the genes have been reported or proposed as causes of disorder of sexual development (DSD) or gonadal failure in humans.

## Workup

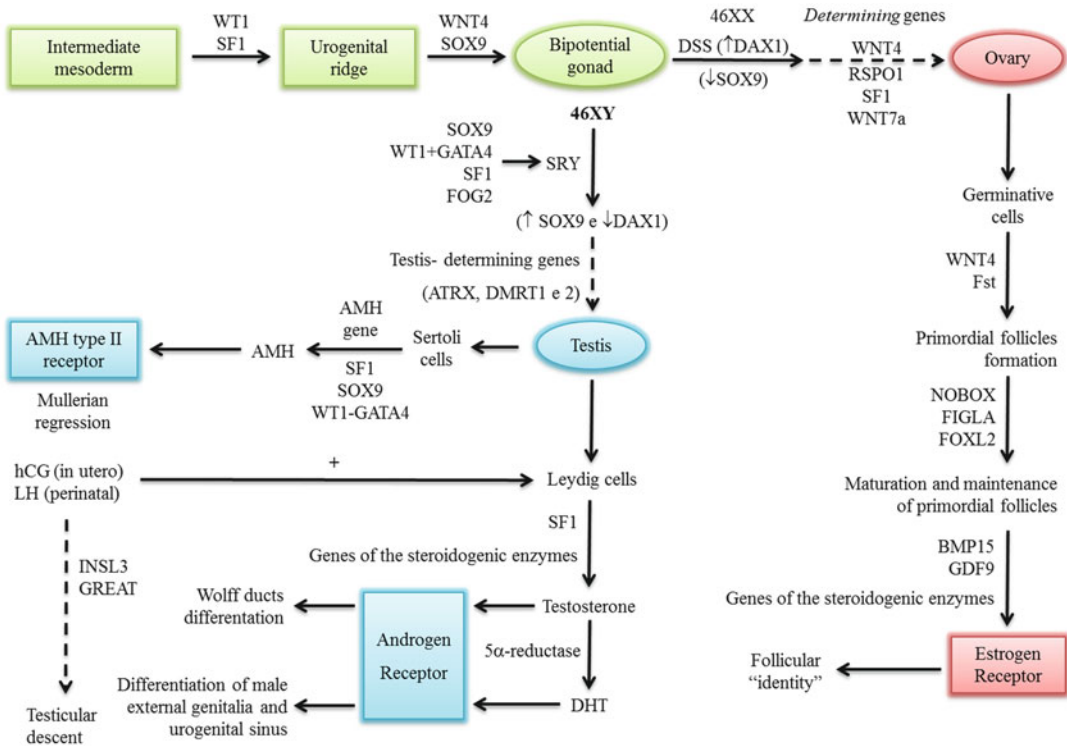
The initial evaluation of a child with DSD includes medical history, family history, physical examination, hormonal secretion assessment, evaluation of internal anatomy, evaluation of ducts by imaging studies, and establishment of genetic sex by karyotype [4].

The clinical presentation is highly variable. Therefore, initially it is important to recognize when a child is suffering from DSD based on the following conditions [4]:

- Obvious ambiguous genitalia.
- Apparently female genitalia with increasing clitoral (more than 6 mm in diameter or more than 9 mm in length), with labial fusion posterior fusion or inguinal/labial mass [5, 6].
- Apparently male genitalia with bilateral cryptorchidism, micropenis (penile length less than  $-2.5$  standard deviations from the mean for child's age or in a term infant, the penile length is  $<2.5$  cm, and penile diameter is  $<0.9$  cm), isolated perineal hypospadias or mild hypospadias with cryptorchidism [5].
- Discordance between phenotype and prenatal karyotyping.

The medical history should include [4]:

- Family history of consanguinity, genital ambiguity, primary amenorrhea, or infertility
- History of perinatal dehydration and/or hypoglycemia and/or death in the family suggests Congenital Adrenal Hyperplasia (CAH) salt wasting.
- Medication virilizing or feminizing during pregnancy (especially in the first trimester) or maternal virilization (suggests a tumor producing androgens by the mother, P450-oxidoreductase deficiency, or presence of placental aromatase deficiency).



**Fig. 19.2** Genes involved in sexual determination and differentiation

The general physical examination should include:

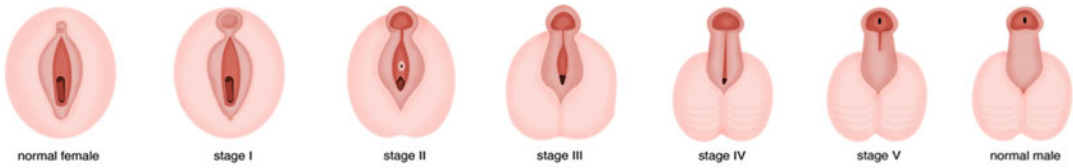
- Features suggestive of malformation syndromes
- Hydration, blood pressure
- Genital examination:
  - Size and differentiation of the phallus
  - Location, size, and consistency of the gonads
  - Position of meatus
  - Genital skin pigmentation (hyperpigmentation suggests increased adrenocorticotrophic hormone), which occurs in CAH.

The Prader classification (Fig. 19.3) may be used to evaluate virilized female genitalia and to classify the external genitalia (see Figs. 19.4 and 19.5).

## Hormonal Assessment

The following hormones should be evaluated on ambiguous genitalia, with the majority being used to diagnose CAH (Fig. 19.6):

- 17OHprogesterone (17OHP)—Evaluate on the second day of life. High levels are useful to diagnosis CAH, CYP21A2, and CYP11B1 defects. Low levels are useful to diagnosis 17 $\alpha$ hydroxylase/17lyase.
  - Pregnenolone/17OHpregnenolone—Defects of 3 $\beta$ -hydroxysteroid dehydrogenase and 17 $\alpha$ -hydroxylase/17lyase, respectively.
  - Dehydroepiandrosterone (DHEA)—Defect of 17 $\alpha$ -hydroxylase/17lyase.
- The following tests are useful to evaluate testes function:
- AMH—Low or undetectable in gonadal dysgenesis (46XY) and in 5 $\alpha$ -reductase defect. Normal or high in androgen insensitivity, LH receptor, and steroidogenic protein defect [7].
  - Human chorionic gonadotropin (hCG) test—hCG has a LH-like function and stimulates testosterone synthesis in testes. There are various protocols for hCG



Stage I: clitoromegaly without labial fusion

Stage II: clitoromegaly and posterior labial fusion

Stage III: greater degree of clitoromegaly, single perineal urogenital orifice, and almost complete labial fusion

Stage IV: increasingly phallic clitoris, urethra-like urogenital sinus at base of clitoris, and complete labial fusion

Stage V: penile clitoris, urethral meatus at tip of phallus, and scrotum-like labia (appear like males without palpable gonads)

**Fig. 19.3** Prader Stages



**Fig. 19.4** Ambiguous Genitalia Prader III

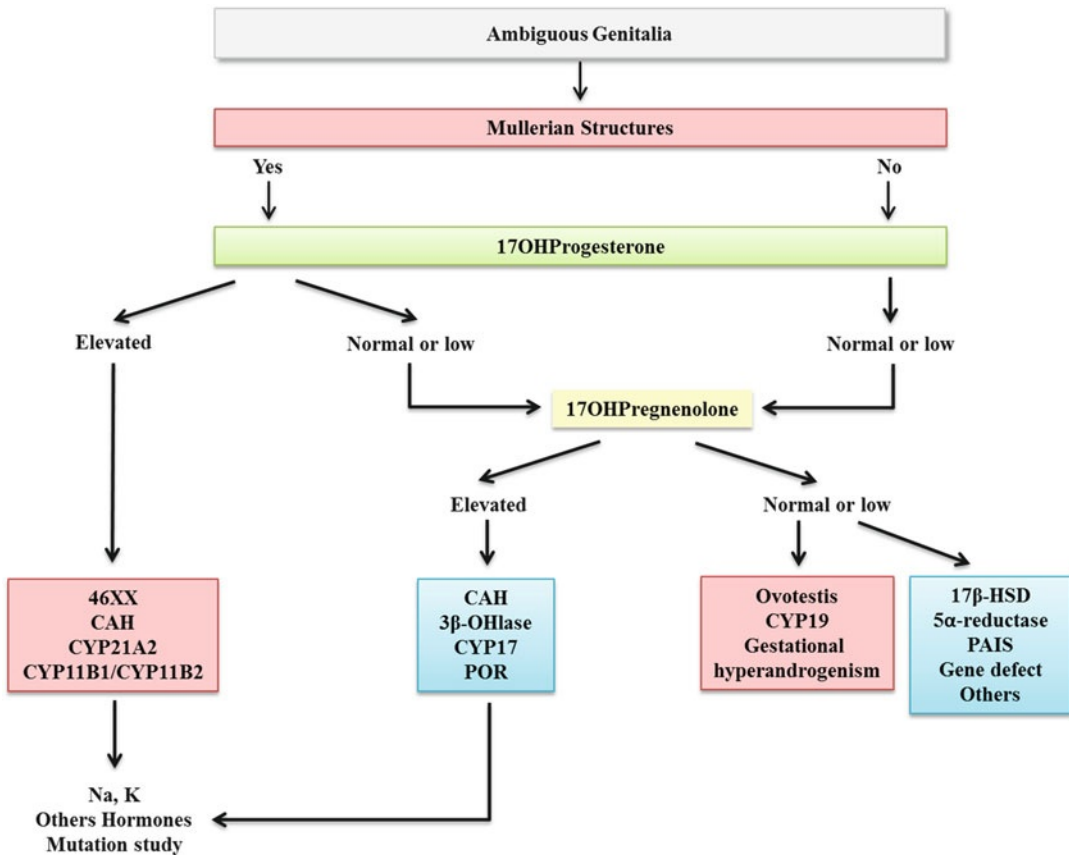


**Fig. 19.5** Ambiguous Genitalia Prader V

stimulation, but intramuscular hCG 1,000–1,500 UI on 3 consecutive days is the most used. Testosterone levels should be done at basal and 24 h after the last dose. Normal response is considered twice the testosterone levels [8].

### Imaging Studies

Ultrasonography (US), genitography, and magnetic resonance imaging (MRI) may be performed if deemed necessary [9].



**Fig. 19.6** Initial Approach to Ambiguous Genitalia

- US is useful to evaluate the presence or absence of gonads and Müllerian derivatives.
- Genitography shows the presence or absence of the vagina, its relationship to the urethra, the level of the external sphincter, and cervical impression. It is helpful to establish the presence and size of the vagina or utricular pouch.
- MRI is more sensitive than US in the evaluation of the gonads and had shown up to 100 % accuracy in detection of the testes [10]. MRI could be reserved for gonad identification when ultrasound examination fails. MRI and genitography are essential for proper pre-corrective surgery assessment.

## Karyotype

Karyotype is performed, usually using peripheral leukocytes and the result will be 46XX, 46XY, 45X or mosaicism.

Ambiguous genitalia are due to gonadal disorders (ovotesticular DSD and gonadal dysgenesis) and according to karyotype are called 46XX DSD or 46XY DSD (which includes malformation syndromes) [4, 11–13].

## Gonadal Disorders

Ovotesticular DSD is a rare condition (4–10 % of cases of DSD). It refers to the presence of

both ovarian and testicular tissue in various combinations in the same individual. This condition has been termed “true hermaphroditism” in the past, and these individuals present mixed ovarian and testicular tissue (either ovotestis, or ovary and testis). Often, the differentiation of internal genitalia coincides with the gonad on the ipsilateral side. The most common karyotype is 46XX, but there are also patients with 46XY or 46XX/46XY [11].

## Gonadal Dysgenesis

In gonadal dysgenesis, a dysgenetic testis or a “streak gonad” replaced the gonad. There are two types: Pure or complete, and partial or mixed.

- Pure gonadal dysgenesis: The neonate will have *streak* gonads and seems female but puberty will be delayed and the child will present with amenorrhea. The karyotype may be 46XX, 46XY, or a Turner syndrome karyotype (45X) [10]. Included in this group is Swyer syndrome with external female genitalia, uterus and fallopian tubes and karyotype 46XY. The cause may be a mutation in the SRY gene, although in the majority of cases, the etiology is unknown [14, 15].
- Partial or mixed gonadal dysgenesis: There is a streak gonad in one side and a dysgenetic testis on the contralateral side. The genotype is 45X/46XY or 46XY. The phenotype depends on the amount of testosterone produced by the dysgenetic testis [16].

## Gonadal Dysgenesis Associated with a Syndrome Phenotype

The mixed sex chromosome also includes 47XXX (Klinefelter syndrome), 45X (Turner Syndrome), and mosaicisms with normal genitalia.

## Embryonic Testicular Regression Syndrome or Vanishing Testes

The testicular tissue regression occurs when the testes are lost during the phase of male differentiation. The penis and scrotum will form and continue to develop, but both testicles will be absent. The phenotype reflects the amount of testosterone produced before the regression.

## Others

A 46XX DSD with evidence of functioning testicular tissue is important to evaluate the presence of genes of the Y chromosome, as it may be caused by translocation of the sex determining region of the Y (SRY) gene [17] or SOX9, SF1, WT1, DHH genes [18]. The diagnosis of SRY translocation can be diagnosed using a fluorescence in situ hybridization (FISH) probe for the SRY gene, and for the SOX9 duplication can be confirmed with a SOX9 FISH probe. These tests are available for either research or clinical evaluation.

## Other Genetic Defects

- Steroidogenesis Factor 1 (SF-1)—agonadism, adrenal hypoplasia with adrenal insufficiency, cryptorchidism, and micropenis.
- Tumor Wilms gene (WT-1)—a transcriptional factor involving gonadal and renal development:
  - WAGR Syndrome—Wilms tumor, aniridia, genitourinary anomalies
  - Denys-Drash Syndrome—A triad: 46XY karyotype, undervirilization, and Wilms tumor.
  - Frasier Syndrome—46XY karyotype, gonadal dysgenesis with female genitalia and renal failure.

The possible etiologies of a DSD are shown on Table 19.1 [19, 20].

**Table 19.1** DSD Classification

DSD due <i>disorders gonadal development</i>	
<ul style="list-style-type: none"> <li>• Ovotestis (karyotype 46XX, 46XY, 46XX/46XY)</li> <li>• Gonadal Dysgenesis (karyotypes 45X/46XX, 45X/46XY, etc.)</li> <li>• Gonadal Dysgenesis associated with syndromic phenotype (45X, 47XXX, etc.)</li> <li>• Embryonic Testicular Regression Syndrome (karyotype 46XY)</li> <li>• Others: SF1, WT1 (WAGR, Denys–Drash and Frasier syndromes)</li> </ul>	
46XX DSD	46XY DSD
Fetal	Defect of Androgens Synthesis
Congenital Adrenal Hyperplasia (CAH)	<ul style="list-style-type: none"> <li>• Associated with cholesterol synthesis defects (Smith–Lemli–Opitz syndrome)</li> <li>• STAR deficiency and P450scc deficiency</li> <li>• 3<math>\beta</math>-hydroxysteroid dehydrogenase 2 deficiency</li> <li>• 17<math>\alpha</math>-hydroxylase and 17,20lyase deficiency (CYP17)</li> <li>• P450-oxidoreductase (POR)</li> </ul>
<ul style="list-style-type: none"> <li>• 21<math>\alpha</math>-hydroxylase deficiency (CYP21A2)</li> <li>• 11<math>\beta</math>-hydroxylase deficiency (CYPB11B1 e CYPB11B2)</li> <li>• 3<math>\beta</math>-hydroxysteroid dehydrogenase 2 deficiency</li> </ul>	
Maternal Fetal	Defect Testicular Steroidogenesis
<ul style="list-style-type: none"> <li>• P450-oxidoreductase deficiency (POR)</li> <li>• Aromatase deficiency(CYP19)</li> </ul>	<ul style="list-style-type: none"> <li>• Isolated 17,20lyase deficiency</li> <li>• 17<math>\alpha</math>-hydroxysteroid dehydrogenase 3 deficiency</li> </ul>
Maternal Hyperandrogenism	Defect of Testosterone Metabolism
<ul style="list-style-type: none"> <li>• Endogenous tumors (Adrenal and ovaries)</li> <li>• Exogenous (progestin and others)</li> </ul>	<ul style="list-style-type: none"> <li>• 5<math>\alpha</math>-reductase type 2 deficiency</li> </ul>
	Defect of Androgen Action
	<ul style="list-style-type: none"> <li>• CAIS</li> <li>• PAIS</li> </ul>
	Persistence of Müllerian Ducts Syndrome
	Others
	<ul style="list-style-type: none"> <li>• Endocrine disruptors</li> <li>• Hypospadias</li> <li>• Cryptorchidism</li> </ul>

## Approach to 46XXDSD

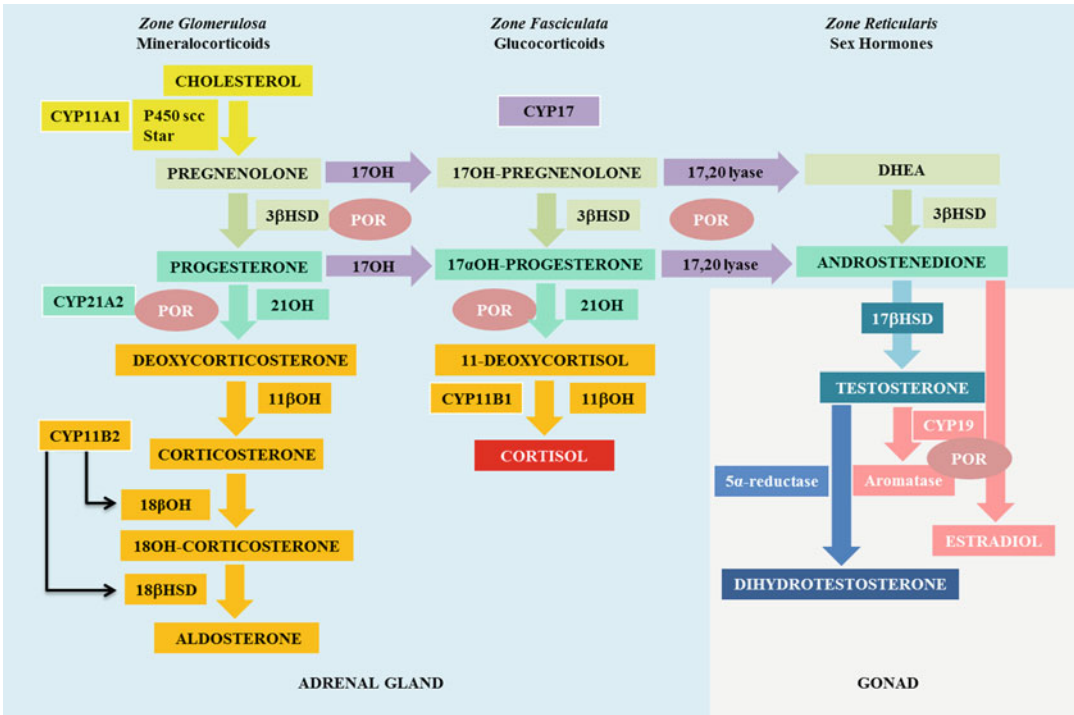
Individuals with 46XX DSD will typically have female internal genitalia (Müllerian structures and ovaries). The differential diagnosis of 46XX DSD includes the disorders of gonadal development previously mentioned. The androgen excess of the fetus is due to CAH or other enzymes or maternal fetal disorders or gestational hyperandrogenism [11, 21].

### Androgen Excess of the Fetus

- CAH: Is a group of autosomal recessive disorders characterized by enzymatic defect in steroidogenesis (Fig. 19.7). The six forms of CAH are summarized in Table 19.2.
- 21 $\alpha$ -hydroxylase (CYP21A2) deficiency is the most common cause of a virilized female infant and occurs in 1:14,000 births, and these babies

have high levels of serum 17OHP. The majority of these infants have salt-wasting, which causes hyponatremia with hyperkalemia and hypotension, and are at risk for the death-threatening complication of adrenal crisis, commonly after the second week of life [22].

- 11 $\beta$ -hydroxylase (CYP11B1 and CYP11B2) deficiency is a second cause of a virilized female infant and hypertension due high levels of deoxycorticosterone (DOC). These infants have also high levels of serum 17OHP and 11-deoxycortisol [23].
- 3 $\beta$ -hydroxysteroid dehydrogenase 2 (HSD3B2) deficiency is a more uncommon cause of ambiguous genitalia in females and may be with or without salt wasting. It is characterized by high levels of pregnenolone/17OHPregnenolone ratio and low levels of 17OHP [23].



**Fig. 19.7** Steroidogenesis. 3 $\beta$ -hydroxysteroiddeshydrogenase (3 $\beta$ HSD), 17 hydroxylase (17OH), 18 $\beta$  hydroxylase (18 $\beta$ OH), 18 $\beta$ hydroxydesidrogenase (18 $\beta$ HSD)

### Maternal Fetal Hyperandrogenism

- P450-oxidoreductase (POR) deficiency presents defects of 21 $\alpha$ -hydroxylase, 17 $\alpha$ -hydroxylase /17,20lyase, and aromatase. It has a variable phenotype, as there are ambiguous genitalia at birth without posterior virilization. The mother was also virilizing during the gestation [21].
- Aromatase (CYP19) deficiency results in an underproduction of estrogen and excess of androgen production. The mother and the 46XX fetus may be virilizing.

### Maternal Hyperandrogenism

The maternal hyperandrogenism may be:

- Endogenous conditions: Maternal tumors of ovaries and adrenals.
- Exogenous: Progestin and others.

### Approach to 46XYDSD

The 46, XY DSD is due to the abnormalities of gonadal development previously mentioned. Impaired androgen production is a consequence of a defect that can occur in all steps of testosterone biosynthesis and secretion.

### Impaired Androgen Production

Neonates with a defect in androgen biosynthesis or metabolism typically have normal testes and no Müllerian structures are formed [11, 24].

- Defect Adrenal Androgen Biosynthesis:
  - Associated with cholesterol synthesis defects: Smith–Lemli–Opitz syndrome.
  - STAR deficiency and P450scc deficiency: results in lipid CAH and under virilization of the genitalia.



- 3 $\beta$ -hydroxysteroid dehydrogenase type II deficiency: results in ambiguous genitalia in males and the hormonal alterations as mentioned previously.
- 17 $\alpha$ -hydroxylase and 17,20lyase deficiency (CYP17): ambiguous genitalia with high levels of pregnenolone and low levels of DHEA, and hypertension due to high levels of DOC and aldosterone.
- POR deficiency—as mentioned previously.
- Defects of the Biosynthesis of Testosterone:
  - At birth patients present normal female or ambiguous genitalia with:
    - Isolated 17,20lyase deficiency.
    - 17 $\beta$ -hydroxysteroid dehydrogenase III deficiency—occur with virilization at puberty.
- Defect of Testosterone Metabolism
  - 5 $\alpha$ -Reductase type 2 deficiency—the etiology is mutations of the SRD5A2 gene leading to an impaired conversion of testosterone to DHT. An increased testosterone/DHT ratio can be used to establish the diagnosis [25]. The main differential diagnosis is with 17 $\beta$ -hydroxysteroid dehydrogenase III deficiency and partial androgen insensitivity.

### Defect of Androgen Receptor

The androgen receptor defect, also called androgen insensitivity, may be complete (CAIS) or partial (PAIS):

- In CAIS, the external genitalia appear female, and the gonad may be palpable on the inguinal area or in the labia majora, or be intra-abdominal. Sometimes, inguinal hernias (which are undescended testes) are present. The vagina is blind and short. At puberty, the classical signal is an absence of sexual hair and amenorrhea with normal breast development.
- PAIS is a heterogeneous syndrome with variability feminization and virilization [26].

### Persistence of Müllerian Ducts Syndrome

Patients have a male phenotype with bilateral cryptorchidism, inguinal hernia, and Müllerian ducts (uterus and fallopian tubes). The persistence of Müllerian ducts is consequence for an AMH gene or its type II receptor mutation [27].

### Non-classified Forms of 46XYDSD

These DSD courses with normal hormonal levels:

- Endocrine Disruptors: environment chemicals may affect the development of the male reproductive tract during fetal life.
- Hypospadias: is a common pathology, and in 40 % of patients is associated with other defects of the urogenital system. It sometimes indicates that there was an alteration of testosterone secretion *intra-uterus* [24].
- Cryptorchidism: undescended testes may be a consequence of testosterone secretion alterations *intra-uterus*. It may be unilateral or bilateral and localization may be outside the external ring (suprascrotal), followed by the inguinal canal, and finally the abdomen. Patients who have cryptorchidism and hypospadias have an increased risk of having a DSD.

### Present and Future Therapies

The patient with ambiguous genital should be identified soon after birth and be evaluated by an expert in DSD who works, preferentially, in a multidisciplinary team. The Chicago Consensus 2006 [28] recommends that the ideal team includes endocrinology, surgery or urology or both, psychology/psychiatry, gynecology, genetics, neonatology, and, if available, social work, nursing, and medical ethics. In clinical practice, this is not always possible since ambiguous genitalia is uncommon condition, but the interaction and expertise of the health professionals are fundamental to the well-being of parents and, hereafter, of the children.

**Table 19.2** Congenital Adrenal Hyperplasia

Enzymatic defect	Lipoid hyperplasia	3 $\beta$ -hydroxysteroid dehydrogenase 2	21 $\alpha$ -hydroxylase	11 $\beta$ -hydroxylase	17 $\alpha$ -hydroxylase	P450-oxidoreductase
Gene	StAR CYP11A1	HSD3B2	CYP21A2	CYP11B1	CYP17	POR
Gene localization	8p11.2/15q23-24	1p13.1	6p21.3	8q24.3	10q24.3	7q11.2
Ambiguous genitalia	Male	Male	Female	Female	Male	Male/female
Postnatal virilization	No	Yes	Yes	Yes	No	No
Frequency	Rare	Rare	1:14,000	1:100,000	1:50,000	Rare
Hormones	Glucocorticoids ↓	↓	↓	↓	↓	Normal ↓ after ACTH
Mineralocorticoids	↓	↓	Normal or ↓	↑	↓	Normal or ↓
Androgens	↓	↓ (♂) ↑ (♀)	↑	↑	↓	↓ (♂) ↑ (♀)
Elevated Metabolite	None	DHEA	17OHP	DOC	DOC	Pregnenolone
Blood pressure	↓	Pregnenolone ↓	Progesterone Normal or ↓	11-deoxycortisol ↑	Pregnenolone ↑	Progesterone Normal
Sodium	↓	Normal or ↓	Normal or ↓	↑	↑	Normal
Potassium	↑	Normal or ↑	Normal or ↑	↓	↓	Normal

In 2012, Moran and Karkasis proposed a protocol to guide this team formation. Despite the wide range of diagnostic possibilities in the patient with ambiguous genitalia, the psychosocial support is essential for all of them [29]. The education of the professionals that provide the initial care to the newborn and the family is important for the next clinical approach.

During the first interview, care should be taken to avoid terms that increase the suspense for the parents (use always neutral term: “the baby,” ...), and the interview should ascertain knowledge parents might already have about their baby’s condition. It has to be clarified that this condition is a consequence to a problem in the complex system of genital development and is nothing that parents did or did not do. The family should be advised that although it is disturbing and stressful not to know the gender of their baby, this decision will be taken with prudence and based on some examinations could take days or months. They need to know that the initial goal is to determine if there is a life-threatening condition that requires specific urgent treatment. Most patients with ambiguous genitalia do not need medical therapy to be started immediately, with CAH (a more frequent DSD) being the exception.

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## Medical Treatment

*CAH*: the most common form is CYP21A2 deficiency, accounting for more than 90 % of the cases [30]. In this form the therapy consists controlling the cortisol deficiency and suppressing adrenocorticotropic hormone (ACTH) overproduction with glucocorticoid replacement.

- Glucocorticoid Replacement:
  - Glucocorticoid is important in decreasing the stimulation of the androgen pathway, thus preventing further virilization and allowing normal growth and development.
  - Hydrocortisone is the preferred treatment in children due its short half-life and lesser growth suppressive effects. Usual doses in newborn and infancy are 10–15 mg/m<sup>2</sup>/day divided into two to three doses per day [30]. It should be administered as tablets crushed and mixed with a small amount of liquid at the time of administration. The prepared suspensions are not stable [31]. A new delayed- and extended-release hydrocortisone is a promising treatment for CAH [32]. The continuous subcutaneous hydrocortisone infusion may be a valuable adjunct to therapy in those that require high doses of oral hydrocortisone [33].
- When hydrocortisone tablets are not available or in noncompliance patients, long-action glucocorticoid replacement can be used. Despite the 2010 Endocrine Society practice guidelines [30] discouraging chronic usage of long-acting glucocorticoids in children, because of the potential for growth suppression, their use has been studied in small subgroups [34]. In particular, prednisolone in doses of 1.5–3 mg/m<sup>2</sup>/day once-a-day should be considered because it is commercially more available and its suspension formulation may allow better dose titration [35].
- To reduce markedly androgens adrenal levels in some infants, the recommended doses need to be exceeded and then rapidly returned to the maintenance dose to avoid glucocorticoid excess[36].
- Mineralocorticoid Replacement:
  - Approximately one-third of the CAH population will have the classic salt wasting form of the disease and also require mineralocorticoid replacement and sodium chloride. The Consensus recommends these replacements for all patients with the classic form, especially during newborn period and early infancy [30].
  - Mineralocorticoid in the form of fludrocortisone tablets (dose 0.05–0.2 mg/day) are used [34].
  - The dose of sodium chloride supplements is 1–2 g/day divided into several feedings.
- Monitoring Therapy
  - The clinical management of classical CAH is difficult. Therapy is monitoring with hormones measurements and regular physical examination (particularly genitalia, height and weight).

- In children, height and weight should be recorded in each follow-up visit.
- The 17OHP levels normalization usually reflects overtreatment and it is not a treatment goal. Instead, adrenal androgens (androstenedione and testosterone in girls and boys pre-pubertal) are better as therapy adjustments.
- The bone age should be taken annually after age 2 years to estimate the skeletal maturation.
- Patients with salt-wasting CAH also require sodium, potassium, and plasma renin activity monitoring.
- Medical therapy during stress:
  - The patient and the family should be given information about increasing (2–3 times) glucocorticoid dosage in situations of febrile illness (>38.5 °C), gastroenteritis with dehydration, surgery, and trauma. Emotional or mental stress, minor illnesses, and before physical exercise do not require a stress dose [30]. Other steroid delivery methods (suppositories and intramuscular injections) may be needed in an emergency.
  - Recommended intramuscular hydrocortisone doses are 25 mg for infants, 50 mg for children over age 4 years and 100 mg for all others. During surgical procedures, stress doses should be administered as continuous or successive (3–4 times/day) intravenous infusion.

*Other causes:* other causes of ambiguous genital do not require specific medical treatment in infancy. In general, appropriate hormone replacement is initiated at the time of physiological puberty in patients with hypogonadism. Before this time, it is important for the patient to make regular visits to pediatric endocrinologist for information about replacement therapy, updates on new therapies, and outcomes and warranty for long-term adherence to treatment.

- Hormonal Replacement:
- Hormonal replacements should attempt to replicate physiological puberty (normal secondary sexual characteristics, growth spurts and optimal bone mineral accumulation).

- Females:

Usually the induction of puberty is between 10.5 and 12 years of age. They require low-dose of estrogen supplementation (0.3 mg of conjugated estrogens every other day or 5 µg of ethinyl estradiol daily) initially to avoid excessive acceleration of skeletal maturation [30, 37].

The estrogen dose can be increased in 6–12 month intervals.

A transdermal patch cut may be used [38].

A progestin should be added after breakthrough bleeding or within 1–2 years of estrogen replacement [30, 37].

- Males:

Induction of puberty begins at 12.5–14 years.

Depot intramuscular testosterone esters (enanthate or cypionate) are used at a dosage of 25–50 mg every 4 weeks.

The dosage and frequency should be increased over 3–4 years to a full replacement [36].

The new testosterone formulations (patch, gel, transbuccal and long-acting) provide fixed and high dosages to induce puberty and they are difficult to handle in adolescence [39].

---

## Gender of Rearing

After disorders affecting glucocorticoid and mineralocorticoid biosynthesis are identified and, who presents a risk of death, the gender for rearing needs to be decided. For parents this is the more distressing situation [30, 40]. Factors that influence the decisions regarding the appropriate gender of rearing include:

- Diagnosis
  - Specific pathophysiology of the diagnosis
  - Genital appearance
  - Surgical options
  - Capacity for spontaneous pubertal development and sexual activity
  - Potential for fertility
  - The view of the family and circumstances relating to cultural practices to these factors
- How to decide the gender for rearing:
- Majority of 46XX CAH patient identify as female and this gender of rearing is recommended. Controversies exist in those with

Prader stage IV or V, who were androgen exposed to the central nervous system *intra-uterus*, as this affects their gender identity [41]. More studies are necessary to evaluate this topic, but it is reasonable that most patients with 46XX CAH should be assigned the female gender because of the potential for fertility.

- All patients with CAIS are assigned a female gender. About 25 % of patients with PAIS are dissatisfied with the gender of rearing, whether raised male or female [42]. The clinical response of testosterone (one or more intramuscular injections with 25 mg testosterone depot) can aid in this decision-making process.
  - Approximately 60 % of 5 $\alpha$ -reductase deficient patients are assigned the female gender in infancy but virilize at puberty and identify as male [25]. In these patients the male gender of rearing is recommended, including the potential for fertility [43, 44].
  - About half of those with 17 $\beta$ -hydroxysteroid dehydrogenase type 2 deficiency self-reassign from female to male [45].
  - The Consensus recommends male rearing in all patients with a micropenis, because there is a similar satisfaction with the assigned sex in those raised male or female. Surgery is not necessary and there is the potential fertility [28].
  - For individuals with mixed gonadal dysgenesis, phallic development, gonadal location, and the ability of secrete testosterone after hCG stimulation to gender assignment should be considered.
  - The decision on gender of rearing in ovotesticular DSD should consider the potential for fertility based on gonadal differentiation and genital development, and assuming the genitalia are, or can be made, consistent with the chosen sex [28].
- Girls with mild and moderate clitoromegaly do not need surgery because of the potential risk of compromising genital sensitivity. The parents should be informed that with glucocorticoid treatment, the stimulated genital tissues would regress.
  - When the multidisciplinary team and parents agree on surgery, this should be performed as soon as possible (ideally between 3 and 9 months of life) [46].
  - The surgery proposal depends on the magnitude of clitoromegaly, posterior fusion and location of the urethral outlet.
  - The clitoroplasty is now well standardized and preserves the neurovascular bundle to maintain clitoral sensitivity [46].
  - Early vaginoplasty should be done in those where the urogenital sinus is high to decrease the risk of recurrent urinary infection. The vaginal reconstruction surgery should provide adequate sexual function with a minimal need for continual dilatation or lubrication.
  - The parents need to know that the adolescent may require vaginal dilatation and some cases need repeat intervention.

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## Surgery Management

An experienced surgeon should discuss the risks and benefits of surgery with the parents.

- Female:
  - The timing and magnitude of this surgery in girls with CAH has been subject for debate in recent years.

- Male:
  - For the undervirilized male, the parents need to be a partner in the surgery decision. The therapeutic surgery goals are adequacy of genital development with the capacity to stand to urinate and to undertake sexual activities.
  - Generally hypospadias, particularly severe, require correction in surgical stages.
  - If there is a cryptorchidism, an orchidopexy should be performed in the first year of life.
  - For patients with the Y in a karyotype raised female, gonadal removal we need to be considered because of the relative risk for gonadal tumors in adulthood. The Consensus suggests testis removal at time of diagnosis in females with CAIS and PAIS [28]. The parents should be informed that the earliest reported malignancy in androgen insensitivity is at 14 years of age [47] so that they can postpone the surgery to the adolescence.

- The streak gonadal in an assigned male should be removed in early childhood.
- Patient with bilateral ovotestis have functional ovarian tissue and potential fertility. Ideally, in early life, the removal of testicular tissue should be done, but this is virtually impossible.
- Utricle and Müllerian remnants should be removed in symptomatic cases [28].

There are so much controversy surrounds the ethical aspects of the validity of parental consent for genital surgery and the removal of gonadal tissue carried out during infancy or childhood. The solution that could protect the human rights and best interests of children is an ongoing challenge [48].

## Psychosocial Support

During childhood, the majority of DSD do not require medical treatment but support from social workers, psychologists, and psychiatrists who are experts in these conditions is important for parents and patients so that they are able to making decisions. The specific support groups are helpful too. The main goal is to promote positive adaptation. These health workers should identify the families with risk for maladaptive behavior and intercede promptly. Although there have been recent advances in genetic research in DSD, we need more outcome data, particularly in regard to sex assignment, as this will guide the medical decision and increase the quality of life, adjustment, and sexual function of these patients [49].

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## Etiology

Hypercalcemia has various causes, although roughly 90 % of cases are caused by primary hyperparathyroidism (pHPTH) (the most frequent cause in outpatients) and malign neoplasias (in hospitalized patients) [1, 4–6]. Other causes of hypercalcemia are less common. Hypercalcemia occurs through a combination of excess bone resorption, an increase in intestinal absorption of calcium, and a decrease in renal excretion. In some disorders, more than one mechanism may be involved, although it is common in almost all hypercalcemic disorders to find an increase in bone resorption (Table 20.1).

## Primary Hyperparathyroidism

pHPTH is a disorder that results from the hypersecretion of the parathyroid hormone. Most cases are sporadic, although around 5–10 % correspond to familiar forms that can be isolated or associated with dominant autosomal hereditary endocrine diseases, such as multiple endocrine neoplasia type 1 (MEN 1) and type 2A (MEN 2A). Its inci-

dence increased significantly in some countries from the mid-1970s onwards with the beginning of systematic measurement of serum calcium. Hypercalcemia in this disorder occurs because of activation of the osteoclasts mediated by the parathyroid hormone culminating in an increase in bone resorption. pHPTH occurs more frequently because of the presence of parathyroid adenoma (~85 %), less frequently owing to a parathyroid hyperplasia (~15 %), and, in rare cases, as a result of parathyroid carcinoma (<1 %) [7]. Patients may develop small increases in serum calcium (increases lower than 11 mg/dl or 2.75 nmol/L) or intermittent hypercalcemia [8–10].

## Secondary and Tertiary Hyperparathyroidism

Patients with chronic kidney disease and secondary hyperparathyroidism usually have normal or low levels of serum calcium although, as the disease progresses, they may develop hypercalcemia. The increase in serum calcium occurs more frequently in patients with adynamic bone disease and a marked reduction in bone turnover. Hypercalcemia is found in these patients because of a marked reduction in the capture of calcium in the bone, as occurs after the ingestion of calcium carbonate to treat hyperphosphatemia [11].

In other patients with advanced-stage kidney disease hypercalcemia derives from the autonomous production of PTH, a disorder known as tertiary hyperparathyroidism.

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**Table 20.1** Etiology of hypercalcemia

Bone resorption	Calcium absorption	Decrease in the excretion of calcium
<ul style="list-style-type: none"> <li>• pHPTH</li> <li>• Malignancy</li> <li>• Thyrotoxicosis</li> <li>• Immobilization</li> </ul>	<ul style="list-style-type: none"> <li>• Milk alkali syndrome</li> <li>• Hypervitaminosis D</li> <li>• Granulomatous disease</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic kidney disease</li> <li>• Rhabdomyolysis and acute renal failure</li> <li>• Thiazide diuretics</li> </ul>
Downregulation of the calcium receptor sensor	Medication	Endocrinal disorders
<ul style="list-style-type: none"> <li>• FHH</li> </ul>	<ul style="list-style-type: none"> <li>• Lithium</li> <li>• Hypervitaminosis A</li> </ul>	<ul style="list-style-type: none"> <li>• Pheochromocytoma</li> <li>• Adrenal insufficiency</li> </ul>

*pHPTH* primary hyperparathyroidism, *FHH* familial hypocalciuric hypercalcemia

## Malignancy

Malignant neoplasias are the most frequent cause of hypercalcemia in hospitalized patients [12, 13]. The frequency oscillates between 10 and 20 % in cancer patients, and may be as high as 40 % in some samples, depending on the duration of the disease, primary site, presence of metastases, and type of malignity.

In the case of solid tumors, the greatest risk of developing hypercalcemia is found with breast and lung neoplasias. This is also the case with tumors in the kidneys, esophagus, and uterus; epidermal tumors; and cholangiocarcinoma. The hematological cancers most likely to develop hypercalcemia are multiple myeloma and lymphoma.

The mechanism for increasing bone resorption in cases of malignant tumors depends on the type of cancer and the presence or not of bone metastases. In patients with bone metastases it is common to find local osteolysis through the direct induction of the tumor cells. Cytokines, such as tumor necrosis factor and interleukin 1, appear to play an important role in differentiating osteoclast precursors in mature osteoclasts [14].

The main cause of hypercalcemia in patients with solid non-metastasized tumors is the secretion by tumors of peptide related to the parathormone (PTH-rP) [14]. In patients with lymphoma hypercalcemia is due to the extrarenal production of calcitriol from calcidiol (irrespective of the PTH) through the activation of mononuclear cells (macrophages). Finally, the ectopic secretion of PTH is a rare cause of hypercalcemia, which has been documented in only a handful of patients.

In general, the consumptive malignity syndrome precedes the pattern of hypercalcemia, which tends to be more severe than that found in pHPTH.

Levels higher than 13 mg/dl (3.25 nmol/L) are generally observed. Hypercalcemia is associated with a low life expectancy in patients with neoplasias, regardless of how well calcemia responds to treatment.

## Thyrotoxicosis

Mild hypercalcemia is seen in around 15–20 % of patients with thyrotoxicosis [15, 16]. The thyroid hormone has bone resorption properties, causing a state of high bone turnover, which may culminate in osteoporosis. Hypercalcemia typically disappears following correction of hyperthyroidism. If hypercalcemia persists after the restoration of normal thyroid activity, we need to measure the serum PTH in order to evaluate the accompanying hyperparathyroidism.

Another less frequent cause of hypercalcemia due to increased bone resorption is immobilization by a high-turnover bone disease, such as occurs in Paget's disease.

A high ingestion of calcium is, in isolation, a rare cause of hypercalcemia, since the initial increase in serum concentrations of calcium inhibits the release of PTH, as well as the synthesis of calcitriol, despite the fact that, when combined with reduced urinary excretion, it may lead to hypercalcemia.

## Alkaline Milk Syndrome

In the absence of kidney failure, hypercalcemia may occur after the ingestion of large quantities of calcium with absorbable substances (sodium bicarbonate and calcium carbonate), leading to

hypercalcemia, metabolic alkalosis, kidney failure, and, usually, nephrocalcinosis. This condition is known as the alkaline milk syndrome [17, 18]. It typically occurs when excess calcium carbonate supplements have been administered during treatment of osteoporosis or dyspepsia. One study found that this syndrome was responsible for 8.8 % of cases of hypercalcemia between 1998 and 2003 [19]. This is one of the few examples of purely absorptive hypercalcemia.

### **Hypervitaminosis D**

Excess intake of vitamin D is a rare cause of hypercalcemia. The dose of vitamin D needed to induce intoxication varies from patient to patient, reflecting differences in absorption, storage, and metabolism, but serum levels of 25OHD, the principal metabolite of vitamin D, >150 ng/ml, generally indicate intoxication. High serum levels of 1.25(OH)<sub>2</sub>D<sub>3</sub> may be observed after ingestion of calcitriol to treat hypoparathyroidism. Owing to its short half-life, the hypercalcemia induced by calcitriol usually lasts between 1 and 2 days. Suspension of calcitriol treatment and its replacement with a saline solution may be the only treatment necessary in such cases. On the other hand, hypercalcemia caused by the ingestion of large quantities of calcidiol may last for several weeks, since the excess vitamin D is cleared slowly by the organism (weeks to months). Aggressive treatment with glucocorticoids, which antagonize the action of calcitriol, and intravenous bisphosphonates may be necessary [20, 21].

### **Granulomatous Diseases**

Hypercalcemia may be found in around 10 % of patients with sarcoidosis and an even higher percentage of these individuals develop hypercalciuria. The main hypercalcemia disorder in these cases is the extrarenal activation of 25-dihydroxyvitamin D by 1 $\alpha$ -hydroxylase in the activated macrophage tissue, which is resistant to normal feedback control. Other granulomatous diseases that may cause hypercalcemia through the same mechanisms include the following:

tuberculosis, berylliosis, disseminated coccidioidomycosis, histoplasmosis, hanseniasis, and pulmonary eosinophilic granulomatosis [22]. Although most patients present normal calcium levels, they may have hypercalciuria and their urinary excretion of calcium should be measured as part of the diagnostic investigation. In addition, hypercalcemia and hypercalciuria may not be apparent until calcium and vitamin D are ingested.

### **Chronic Kidney Failure**

It is known that chronic kidney failure in isolation, although associated with diminished calcium excretion, does not lead to hypercalcemia, owing to hyperphosphatemia and decreased synthesis of calcitriol. On the contrary, these patients commonly present hypocalcemia with hyperphosphatemia. Hypercalcemia, however, may be observed in patients receiving calcium carbonate or calcium acetate in conjunction with dietetic phosphate, if they are being treated with calcitriol in an attempt to revert a hypocalcemia or a secondary hyperparathyroidism.

### **Rhabdomyolysis and Acute Kidney Failure**

Hypercalcemia has been described during the diuretic phase of acute kidney failure frequently seen in patients with rhabdomyolysis. The hypercalcemia is caused by the mobilization of calcium from the damaged muscle [23].

### **Thiazide Diuretics**

The administration of thiazide diuretics may increase serum calcium and this cannot be entirely explained by hemoconcentration. Thiazide diuretics are capable of reducing urinary excretion of calcium and are used in the treatment of patients with recurrent hypercalciuria and nephrolithiasis. Rarely do they cause hypercalcemia in healthy individuals, but they may do so in patients with an underlying increase in bone resorption, such as those with hyperparathyroidism.

## Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is a rare dominant autosomal disorder that is characterized by a genetic defect in the calcium receptors of the parathyroid glands and the kidneys. It leads to mild hypercalcemia and the most striking laboratory finding is hypocalciuria, suggesting tubular resorption of the excess calcium. The level of calcium in urine is generally  $<50$  mg/24 h and the calcium/creatinine clearance ratio  $<0.01$  [24]. This diagnosis should be considered in asymptomatic patients with mild-to-moderate hypercalcemia, who are hypocalciuric and have a family history of hypercalcemia. Its importance as a diagnostic tool is that it provides a differential diagnosis for pHPTH as a way of avoiding unnecessary surgery.

## Lithium

Patients who are long-term users of lithium may develop mild-to-moderate hypercalcemia, probably owing to increased secretion of PTH, through an increase in the levels at which calcium inhibits the release of PTH. The hypercalcemia usually, but not always, goes into remission when treatment is interrupted. Treatment with lithium may also unmask a pattern of HPP; it may, on the other hand, increase serum concentrations of PTH without, however, altering the calcemia [25].

## Hypervitaminosis A

Excessive ingestion of vitamin A ( $>50,000$  UI/d) leads to an increase in bone resorption, culminating in osteoporosis, fractures, hypercalcemia, and hyperostosis. The mechanism by which vitamin A stimulates bone resorption is still not fully clear [26].

## Pheochromocytoma

Hypercalcemia is a rare complication of pheochromocytoma. NEM-2A may occur as a result

of hyperparathyroidism or the pheochromocytoma itself. In this case, the hypercalcemia may be due to the tumor producing PTH-rp. Its concentration in serum may be reduced with the use of  $\alpha$ -adrenergic blockers, suggesting that  $\alpha$ -adrenergic stimulation plays a role in the etiology of the disease [27].

## Adrenal Failure

Hypercalcemia may be a finding in an adrenal crisis. Multiple factors appear to contribute to hypercalcemia, among which are the following: an increase in bone resorption, an increase in tubular resorption of calcium, hemoconcentration, and an increase in calcium-protein bonding. The use of glucocorticoids reverts the hypercalcemia [28, 29].

## Uncommon Causes

In certain situations, the differential diagnosis for hypercalcemia may be a genuine challenge in clinical practice for the endocrinologist and general physician. In the following pages we summarize a number of etiologies that are so uncommon that they are not listed in many reviews of hypercalcemia and rarely considered in patients with hypercalcemia of unknown etiology (Table 20.2).

### Hypercalcemia Caused by High Levels of Calcitriol

As with sarcoidosis, tuberculosis, and some fungal infections, other less common diseases characterized by the formulation of granulomas have been associated with secondary hypercalcemia at high levels of 1,25-dihydroxyvitamin D. Among these are Wegener's granulomatosis, Crohn's disease, catch scratch fever, acute granulomatous pneumonitis (a rare complication of treatment with methotrexate), hepatic granulomatosis, and others [30].

### PTH-rP-Induced Hypercalcemia in Benign Diseases

Although humoral hypercalcemia has long been recognized in neoplasias, hypercalcemia resulting from high levels of PTH-rP in a benign

**Table 20.2** Rare causes of hypercalcemia

1. Wegener's granulomatosis
2. Cat scratch fever
3. Crohn's disease
4. Acute granulomatous pneumonia
5. SLE
6. HIV-associated lymphadenopathy
7. Lymphedema of chest and pleural cavities
8. Massive mammary hyperplasia during pregnancy
9. Omeprazole in acute interstitial nephritis
10. Theophylline toxicity
11. Parenteral nutrition
12. Fosarnet
13. Eosinophilic granuloma
14. Leprosy in rheumatoid arthritis
15. Mycobacterium avium complicating AIDS
16. Cytomegalic virus infection in AIDS
17. Chronic berylliosis
18. Nocardia asteroides pericarditis
19. Diffuse osteoclastosis
20. Brucellosis

Adapted from [30]

disease is very uncommon. This situation has been described in one patient with systemic lupus erythematosus (SLE) with the involvement of multiple organs, lymphadenopathy associated with HIV, diffuse mammary hyperplasia in pregnancy, and benign ovarian and kidney tumors among others [30].

## Clinical Manifestations

The increase in serum calcium causes changes in all organ systems, since its extracellular levels impair the tissue function of the brain, peripheral nerves, smooth visceral musculature, and cardiac and kidney muscles. The severity of the clinical manifestation does not depend exclusively on the level of serum calcium, but on the speed of onset, age, clinical conditions, presence of metastases, liver and kidney failure, and progression of the underlying disease (Table 20.3).

## Gastrointestinal

Intestinal constipation is the most frequent complaint. Other symptoms include anorexia, nausea,

vomiting, and vague abdominal complaints. On rare occasions severe hypercalcemia may cause acute pancreatitis [31–33].

## Renal

The most important renal manifestations are nephrolithiasis, tubular renal dysfunction, and kidney failure, which may be acute or chronic. Chronic hypercalcemia leads to a defect in the ability of urine to concentrate and may give rise to polyuria in up to 20 % of patients, although the mechanism that causes this is unclear. Chronic hypercalcemic nephropathy has the clinical characteristics of an interstitial nephritis with polyuria, natriuresis, and hypertension. Hypertension, nephrolithiasis, obstruction, and possible infections may contribute to an additional loss of kidney function [34].

## Cardiovascular

In chronic hypercalcemia, deposits of calcium may be observed in the heart valves, coronary arteries, and myocardial fibers.

A shortened QT is also found, which does not seem to be clinically important for the functioning of the heart or for the prevalence of supraventricular or ventricular arrhythmias [35–37].

## Neuropsychiatric

The most common neuropsychiatric symptoms are anxiety, depression, and cognitive impairment. More severe symptoms are found in elderly patients with intense hypercalcemia. There may be personality changes and emotional disturbances when concentrations of calcium exceed 12 mg/dl (3 nmol/L), while confusion, psychosis, hallucinations, drowsiness, and coma are rare [38, 39].

## Physical Findings

There are no specific physical findings for hypercalcemia, apart from those that may be related to an underlying disease, such as malignancy

**Table 20.3** Clinical manifestations

Gastrointestinal	Renal	Cardiovascular	Neuropsychiatric	Musculoskeletal
<ul style="list-style-type: none"> <li>• Constipation</li> <li>• Anorexia</li> <li>• Nausea</li> <li>• Peptic ulcer disease<sup>a</sup></li> <li>• Acute pancreatitis<sup>a</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Nephrolithiasis</li> <li>• Nephrogenic DI</li> <li>• Renal tubular acidosis (type I)</li> <li>• Tubular renal dysfunction</li> <li>• Renal insufficiency</li> <li>• Chronic hypercalcemic nephropathy</li> <li>• Nephrocalcinosis</li> </ul>	<ul style="list-style-type: none"> <li>• Shortened QT interval</li> <li>• Deposition of calcium in heart valves, coronary arteries, and myocardial fibers</li> <li>• Hypertension</li> <li>• Cardiomyopathy</li> </ul>	<ul style="list-style-type: none"> <li>• Anxiety</li> <li>• Depression</li> <li>• Cognitive dysfunction</li> <li>• Lethargy</li> <li>• Confusion<sup>a</sup></li> <li>• Stupor<sup>a</sup></li> <li>• Coma<sup>a</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Muscle weakness</li> <li>• Bone pain<sup>b</sup></li> </ul>

DI diabetes insipidus

<sup>a</sup>Rare

<sup>b</sup>Primary hyperparathyroidism or malignancy

syndrome. Ceratopathic bands reflect the deposit of calcium phosphate in the subepithelial portion of the cornea, although this is a very rare finding, normally discovered by means of an ophthalmological examination using a slit lamp [40].

## Diagnostic Evaluation/Laboratory Diagnosis

Hypercalcemia is a relatively common clinical problem. As with most cases of hypercalcemia, it is caused by pHPPTH or malignant disorders, and the laboratory diagnosis typically involves distinguishing between these two clinical conditions. Generally speaking, it is not difficult to differentiate them. Symptoms of malignancy are frequently present at the time of diagnosis of hypercalcemia and serum levels of calcium are normally higher than those in patients with pHPPTH (Table 20.4).

A single high-serum calcium value is not a sufficient diagnosis of hypercalcemia and the measurement should be repeated to confirm the diagnosis, preferably without the use of a tourniquet. If available, previous serum calcium levels should be reviewed. The presence of asymptomatic hypercalcemia of long duration suggests pHPPTH and also increases the likelihood of familial hypercalcemic hypocalciuria. The degree of hypercalcemia may also be useful for differential diagnosis. pHPPTH is normally associated with mild hypercalcemia (<11 mg/dl). Values of >13 mg/dl are more consistent with hypercalcemia resulting from malignant disorders.

In patients with hypoalbuminemia caused by chronic illness or malnutrition, total serum calcium may be normal, although ionizable calcium will be high. In this situation, the serum calcium has to be corrected for the albumin value or, as some prefer, the ionizable calcium measured.

Once hypercalcemia has been confirmed, the next step is to measure serum PTH, in order to distinguish hypercalcemia caused by parathormone (pHPPTH and FHH) from that not caused by PTH (malignant disorders, vitamin D intoxication, granulomatous diseases).

In the case of serum concentrations of PTH below the normal range, PTH-rP should be measured along with 1,25 OH<sub>2</sub>D. If PTH-rP and 1,25 OH<sub>2</sub>D are low, other causes of hypercalcemia should be considered. Additional laboratory data include serum protein electrophoresis to track multiple myeloma, TSH, and vitamin A. In most cases, these laboratory tests lead to the correct diagnosis.

The serum concentration of phosphate and urinary excretion of calcium are also useful for differential diagnosis. pHPPTH and humoral neoplastic hypercalcemia (caused by PTH-rP) frequently present with hypophosphatemia, as a result of the inhibition of resorption of phosphate in the kidneys [2]. On the other hand, the concentration of phosphate is normal or high in granulomatous diseases, vitamin D intoxication, immobilization, thyrotoxicosis, alkaline milk syndrome, and metastatic bone diseases. In familial hypercalcemic hypocalciuria, the levels of phosphate vary [2]. The level of alkaline phosphate (AP) may also be useful in differentiating the causes of hypercalcemia. The AP is high in osteoblastic bone metastasis, as in prostate

**Table 20.4** Interpretation of biochemical and hormonal changes in hypercalcemia

	PTH	PTH-rP	25 OHD	1,25 OH <sub>2</sub> D	Calcium/creatinine
pHPTH	↑	↓	N	N or ↑	>0.02
FHH	N ou ↑	↓	N	N	<0.01
PTH-rP malignancy	↓	↑	N	N or ↓	
Non-PTH-rP malignancy	↓	↓	N	N or ↓	
Granulomatous disease	↓	↓	N	↑	
Hypervitaminosis D	↓	↓	↑	N or ↑	

*pHPTH* primary hyperparathyroidism, *FHH* familial hypocalciuric hypercalcemia

cancer, but not in osteoclastic disorders such as multiple myeloma [22].

Urinary excretion of calcium is usually high in hyperparathyroidism and hypercalcemia associated with malignant disorders. In contrast, there are three disorders in which the increase in resorption of calcium in the kidneys leads to relative hypocalciuria (<100 mg/day or 2.5 nmol/day). These are alkaline milk syndrome, thiazide diuretics, and familial hypercalcemic hypocalciuria, in which the fraction of excretion of calcium is less than 1 % [41, 42].

Finally, it is useful to review the treatment regime (drugs prescribed or not prescribed, use of calcium and vitamin D supplements) and diet for evaluation of alkaline milk syndrome and drug-induced hypercalcemia.

## Treatment

The treatment of hypercalcemia aims to reduce serum concentrations of calcium and, where possible, treat the condition that causes it. Serum levels of calcium can be reduced with measures that act in intestinal absorption, increasing excretion through the kidneys or inhibiting bone resorption. The choice of treatment will depend on the cause and severity of the hypercalcemia (Table 20.5).

Asymptomatic or symptomatic patients with mild hypercalcemia (<12 mg/dl or 3 nmol/L) do not require immediate treatment. Similarly, patients with calcium levels of between 12 and 14 mg/dl may not need immediate treatment, if the hypercalcemia is chronic. However, a sudden rise in the concentration of serum calcium may lead to an altered state of consciousness, thus requiring that more vigorous measures be taken. Patients

with a serum calcium concentration >14 mg/dl need treatment, regardless of the symptoms.

## Increasing Urinary Excretion

Filtered calcium is reabsorbed, mainly in the proximal tubules and the ascending branches of Henle's loop. This process is passive and results in favorable electrochemical gradients created by reabsorption of sodium and chloride. The active resorption of calcium occurs, particularly in the distal tubule under the influence of PTH. The excretion of calcium in urine may be increased in patients with hypercalcemia, thereby inhibiting the resorption of sodium in the proximal tubules and Henle's loop, thus reducing the passive resorption of calcium. Proximal reabsorption is inhibited by volemic expansion with endovenous saline infusion, since this increases the concentration of sodium, calcium, and water in Henle's loop.

Unless the patient has heart or kidney failure, a reasonable regimen is to initiate administration of 200–300 ml/h saline solution, adjusting this to maintain a urinary deficiency of 100–150 ml/h. Only after adequate hydration will it be possible to add 40 mg endovenous furosemide; otherwise the hemoconcentration may worsen. It is known that this loop diuretic blocks the transport of calcium in the proximal tubule. The patient must be monitored to avoid hypovolemia and electrolytic disturbances.

## Reducing Intestinal Absorption

Increase in the intestinal absorption of calcium in the diet is the main mechanism by which the

**Table 20.5** Treatment of hypercalcemia

Agent	Side effects	Administration	Onset of action	Duration of action
Isotonic saline hydration	Volume overload	Saline 0.9 % 200–300 ml/h <i>Cardiac monitoring</i>	Hours	During infusion
Calcitonin	Injection side reactions, flu-like syndrome, nausea, diarrhea, dyspepsia, fatigue, flushing	4 U/kg 12/12 h	4–6 h	48 h
Loop diuretics	Hypocalcemia, hyponatremia, hypomagnesemia, metabolic alkalosis, glucose intolerance, hyperlipidemia	Furosemida 40 IV 12/12H. Begin only after adequate hydration	Hours	During therapy
Glucocorticoids	Cushingoid appearance, weight gain, cataracts/glaucoma, peripheral insulin resistance/hyperinsulinemia, gastritis/ulcer formation/GI bleeding, hypertension, osteoporosis, vertebral fractures, mood disorders neutrophilia	Prednisone 20–40 mg/day	3–5 days	2 weeks
Bisphosphonates	Flu-like syndrome, fever, fatigue, headache nausea/vomiting, anxiety, myalgia, arthralgia hypocalcemia	<i>Pamidronate</i> Begin with doses of 30–90 mg IV, diluted in saline 0.9 % at 2–4-h intervals <i>Zoledronic acid</i> 4–8 mg at 15–30-min intervals	24–72 h	2–4 weeks

administration of excessive quantities of vitamin D or endogenous overproduction of calcitriol leads to hypercalcemia.

Corticoids may be effective in patients with hematological malignant disorders and hypercalcemia associated with excess vitamin D. Glucocorticoids may be particularly effective in cases of myeloma, lymphoma, sarcoidosis, and other granulomatous diseases [43]. In such cases, 20–40 mg/day of prednisone reduces the concentration of serum calcium within 2–5 days, diminishing the production of calcitriol by activated mononuclear cells in the lung and the lymph nodes.

### Inhibiting Bone Resorption

Biophosphonates have become one of the main tools in the treatment of hypercalcemia, especially severe hypercalcemia associated with malignant disorders. These drugs are effective inhibitors of osteoclasts and thus influence one of the most important physiopathological mechanisms in hypercalcemia. The maximum effect occurs within 2–4 days and so they are normally administered along with a saline solution or cal-

citonin when rapid normalization of serum calcium is desired.

Of the agents currently available for treatment of hypercalcemia associated with malignant disorders (pamidronate, zoledronate, ibandronate, clodronate, and etidronate), zoledronic acid and pamidronate are, at present, the treatments of choice for hypercalcemia.

Pamidronate can be used at a dose of 30–90 mg, depending on the initial levels of calcium and are effective in normalizing serum calcium in 70–100 % of cases [44]. The response to treatment is dose dependent and the maximum calcemia normalization effect is seen with an endovenous dose of 90 mg [45]. This is normally administered as a single endovenous infusion diluted in an isotonic saline solution for 4–6 h. A 24-h infusion treatment regimen has also been proposed. The drug is well tolerated with a small incidence of influenza-like symptoms, notably fever. The response is frequently continuous for up to 2–4 weeks, with maintenance of normal calcemia for up to 15 days [46–48].

Trials have shown that pamidronate (60 mg in 24 h) is more effective in reducing hypercalcemia associated with malignant disorders than



etidronate (70×41 %) and clodronate [49, 50]. Subsequent trials have shown that pamidronate is also safer, has a shorter infusion time, and is more effective in maintaining normal levels of calcemia [51, 52].

Zoledronate has been shown to be the most powerful bisphosphonate in the treatment of hypercalcemia, especially when associated with malignant disorders. In a study carried out with 275 patients with hypercalcemia associated with malignancy (moderate to severe), the efficacy and the maintenance of the response to treatment with zoledronate at doses of 4 and 8 mg were compared with those of pamidronate, at a dose of 90 mg. Zoledronic acid was administered at doses of 4 and 8 mg in 5-min endovenous infusions, while pamidronate was infused at a dose of 90 mg for 2 h. This study concluded that both doses of zoledronate were superior to pamidronate. The rate of normalization of calcemia on the tenth day was 88.4 % with 4 mg and 86.7 % with 8 mg of zoledronate compared with 69.7 % with 90 mg of pamidronate. Normalization of calcium levels occurred on the fourth day in approximately 50 % of patients treated with zoledronate compared with 33.3 % of those who took pamidronate. The mean duration of control was longer with zoledronate (32 and 43 days), compared with pamidronate (18 days). The authors concluded that zoledronate is superior to pamidronate and the recommended dose is 4 mg, with the 8-mg dose being reserved for stubborn cases or reoccurrences [53].

Although renal toxicity has been reported more frequently with zoledronate than with pamidronate, in trials that evaluate the chronic use of these drugs in the treatment of metastatic bone disease, no differences were observed between the drugs with regard to kidney failure. The efficacy of 4 and 8 mg of zoledronic acid was similar, although with the 4 mg dose the incidence of renal toxicity was lower (5.2×2.3 % with 4 mg) [54].

Ibandronate has also been shown to be effective in the treatment of hypercalcemia associated with malignancy. In a study involving more than 320 patients, the 2 mg endovenous dose normalized serum calcium in 67 % of patients and endovenous doses of up to 6 mg were shown to be safe and well

tolerated [55, 56]. The frequency of response was significantly higher with 4 or 6 mg than with 2 mg, although the duration of response was not dose dependent.

In a trial involving 72 patients with hypercalcemia associated with malignancy, ibandronate (2–4 mg) was compared with pamidronate (15–90 mg IV). The number of patients who responded to both agents was similar (77×76% for ibandronate and pamidronate, respectively), but ibandronate proved to be more effective in maintaining normal levels of calcemia (14×4 days) [57].

It is known that bisphosphonates are nephrotoxic drugs, although in clinical trials involving zoledronate for treatment of hypercalcemia associated with malignancy patients with levels of creatinine higher than 4.5 mg/dl were considered eligible for the study [53]. Furthermore, there have been three reports of the successful use of both ibandronate and pamidronate in patients with kidney failure and multiple myeloma [58], patients with kidney failure (creatinine>1.5 mg/dl) [59], and patients on hemodialysis with severe hypercalcemia [60, 61]. However, we suggest caution in the use of endovenous bisphosphonates to treat hypercalcemia in cases of kidney failure. The dose of bisphosphonates should be reduced (4 mg of zoledronate, 30–45 mg of pamidronate, and 2 mg of ibandronate) in order to minimize the risk of further deterioration of kidney function.

Salmon calcitonin is another treatment option available for acute hypercalcemia. Like bisphosphonates, it inhibits bone resorption through osteoclasts. It may be administered IM or SC [62]. Intranasal calcitonin has been shown not to be effective for treatment of hypercalcemia [63]. The recommended dose is 4 U/kg every 12 h, with the possibility of increasing the dose to 6–8 U/kg every 6 h [64]. The great advantage of calcitonin is its speed of action, reducing serum calcium in a matter of hours. The maximum reduction in calcium is seen within 12–24 h. It is not a powerful agent and levels of calcium fall at most 1–2 mg/dl; another disadvantage is the development of tachyphylaxis, probably by downregulation of the receptor. It should thus be combined with bisphosphonates to bring about a sharper and more lasting drop in serum calcium levels.

## Other Treatments

### Calcimimetics

Calcimimetic agents (cinacalcet is the only one currently available) reduce the concentration of serum calcium in patients with severe hypercalcemia caused by a parathyroid carcinoma, patients on hemodialysis with an increase in the calcium-phosphorus product, and in cases of secondary hyperparathyroidism. Calcimimetics have been evaluated for treatment of pHPTH, but are not considered to be the standard treatment [65].

### Dialysis

Dialysis, be it hemodialysis or peritoneal dialysis, is an effective way to treat hypercalcemia. Dialysis is particularly useful in patients with kidney and heart failure for whom it is not safe to infuse saline solutions [66].

### New Therapies

It is known that in patients with cancer and creatinine clearance  $<60$  ml/min/1.73 m [2], bisphosphonates can cause a reduction in kidney function in approximately 20 % of cases. The use of these kinds of medication is strongly discouraged in patients with creatinine clearance  $<30$  ml/min/1.73 m [2]. RANKL system inhibitors have emerged as an important treatment option in these cases, denosumab being the most promising drug of this class. These monoclonal human antibodies attach themselves to and neutralize the RANKL, inhibiting osteoclastic activity. As they are metabolized by peptidases and cleared by the reticuloendothelial system, their nephrotoxic effects are minimal [67, 68]. In a study that compared denosumab with zoledronic acid in the treatment of patients with bone metastases, a deterioration of 6–11 % in kidney function was found in patients receiving denosumab 120 mg/month, compared to 20–22 % in those who were receiving zoledronic acid [69].

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## Key Points to the Diagnosis

Serum calcium concentration is determined by the balance between calcium influx into extracellular fluid from intestinal absorption, skeletal resorption, and renal reabsorption and calcium efflux from extracellular fluid through intestinal secretion, skeletal uptake, and renal excretion. Hypocalcemia usually results from decreased skeletal resorption or intestinal absorption, in conjunction with normal or increased renal excretion, but it may result from normal calcium influx in association with increased renal excretion or skeletal mineralization. Decreased skeletal resorption is typically due to decreased osteoclast recruitment and activation, most often due to decreased parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrP), or 1,25-dihydroxyvitamin D levels [3]. Deficiencies of other cytokines that normally stimulate osteoclast recruitment or function, including interleukin (IL)-1 $\alpha$ , IL-1 $\beta$ , IL-6, tumor necrosis factor- $\alpha$ , lymphotoxin, or transforming growth factor- $\beta$ , might also lead to decreased skeletal resorption,

but by themselves do not cause hypocalcemia. Decreased intestinal absorption of calcium is fairly common, typically occurring due to decreased 1,25-dihydroxyvitamin D or malabsorption. Regardless of the cause of decreased calcium influx into extracellular fluid, serum calcium levels do not typically decrease unless the kidneys fail to compensate with appropriately increased urinary calcium reabsorption.

Other factors may indirectly affect serum calcium. Decreased PTH and PTHrP lead to decreased renal tubular reabsorption of filtered calcium, which results in increased urinary calcium excretion. Increased fluid intake may result in hemodilution, and volume overload may result in polyuria resulting in increased renal calcium clearance. Physical activity may directly decrease bone resorption and thereby reduce serum calcium.

The seven-transmembrane G protein-coupled extracellular calcium-sensing receptor (CaSR) plays a major role in regulation of extracellular calcium [4]. This receptor is found on parathyroid, renal tubular, osteoblast, intestinal mucosal, and adipocyte cells, as well as other cells in other tissues. The CaSR regulates secretion of PTH by parathyroid cells and renal tubular reabsorption of calcium, as it regulates bone turnover and intestinal absorption of calcium. The CaSR is a seven-transmembrane segment receptor, with a large extracellular portion that binds ionized calcium, and a shorter intracellular portion that interacts with a variety of G proteins and signal-transduction pathways. It may be part of a larger family of calcium- or cation-binding receptors.

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## Signs and Symptoms

Patients with mild hypocalcemia may be completely asymptomatic, whereas those with severe hypocalcemia are often incapacitated due to profound metabolic derangements. The magnitude of symptoms and signs present depends largely on the severity and chronicity of the hypocalcemia (Table 21.1). Patients with chronically low levels of ionized calcium may be asymptomatic except for a positive Chvostek's sign. Chvostek's sign may be present in up to 15 % of healthy subjects without hypocalcemia, however, so it is not pathognomic of hypocalcemia. Neuromuscular irritability is the most common cause of symptoms, ranging from tingling paresthesias around the fingertips, toes, or lips to tetany, carpopedal spasm, extremity muscle twitching or cramping, or abdominal cramps. Neuromuscular irritability is often most clearly demonstrated by eliciting facial muscle twitching after tapping over the facial nerve just anterior to the ear (Chvostek's sign) [5], or by carpal spasm with inflation of an upper arm blood pressure cuff to 20 mmHg above systolic blood pressure for 3 minutes (Trousseau's sign) [6].

**Table 21.1** Symptoms and signs of hypocalcemia

<i>Symptoms</i>
Circumoral and acral tingling paresthesias
Increased neuromuscular irritability
Tetany
Muscle cramps and twitching
Abdominal cramps
Laryngospasm
Bronchospasm
Altered CNS function
Seizures of all types
Papilledema or pseudotumor cerebri
Choreoathetoid movements
Depression
Coma
Congestive heart failure
Generalized fatigue
<i>Signs</i>
Chvostek's sign
Trousseau's sign
Prolongation of QTc interval
Cataracts
Basal ganglia and other intracerebral calcifications

More severe hypocalcemia may cause bronchospasm, laryngospasm, seizures, cardiac dysrhythmias associated with QT interval prolongation, coma, or sudden death. Head CT or X-ray imaging may demonstrate calcification of the basal ganglia and other intracerebral structures. Patients may develop cataracts related to long-standing treatment-related increases in the calcium x phosphate product, or pseudotumor cerebri. Prolonged hypocalcemia may cause congestive heart failure due to cardiomyopathy, which may reverse with appropriate management of hypocalcemia. Patients often report feeling weak, fatigued, or depressed until hypocalcemia is corrected.

## Differential Diagnosis

Causes of hypocalcemia may be broadly divided into PTH-related and non-PTH-related causes (Table 21.2). PTH-related hypocalcemia is most

**Table 21.2** Causes of hypocalcemia

<i>PTH related</i>
Acquired hypoparathyroidism
Postsurgical
Infiltration with iron
Hemochromatosis
Thalassemia with repeated transfusions
Infiltration with copper: Wilson's disease
Parathyroid metastases
Neck radiation therapy
Hypomagnesemia or hypermagnesemia
Autoimmunity: Parathyroid gland antibodies
Congenital or inherited hypoparathyroidism
APECED syndrome
Autosomal dominant hypocalcemia
Isolated hypoparathyroidism: Familial or X-linked
Parathyroid agenesis
Mutations in PTH gene
Syndromes associated with hypoparathyroidism:
DiGeorge syndrome, mitochondrial disorders with hypoparathyroidism
PTH resistance
Pseudohypoparathyroidism types 1a, 1b, 1c, and 2
Hypomagnesemia
<i>Vitamin D related</i>
Vitamin D deficiency:
Nutritional deficiency
Malabsorption
Lack of adequate sunlight exposure

(continued)

**Table 21.2** (continued)

Hyperpigmentation
Anticonvulsant therapy
Pseudovitamin D deficiency rickets (vitamin D-dependent rickets type 1)
Chronic renal disease
Severe liver disease
Vitamin D resistance
Hereditary vitamin D-resistant rickets (vitamin D-dependent rickets type 2)
<i>Others</i>
Hyperphosphatemia
Chronic renal failure
Tumor lysis syndrome
Rhabdomyolysis
Acute pancreatitis
Burns
Hungry bone syndrome
Osteoblastic bone metastasis
Transfusion with citrated blood products
Critical illness
Pseudohypocalcemia: Gadolinium-based contrast agents: gadodiamide and gadoversetamide B
Medications
Hypocalcemia with decreased PTH levels
Drug-induced hypomagnesemia: Cisplatin, diuretics, aminoglycosides, amphotericin
Drug-induced hypermagnesemia: Magnesium-containing antacids or laxatives, tocolytic therapy
Cinacalcet
Alcohol abuse
Hypocalcemia with increased PTH levels
Calcium-chelating agents: EDTA, citrate, foscarnet, hydrofluoric acid
Vitamin D deficiency or resistance: Phenytoin, phenobarbital, carbamazepine, valproate, isoniazid, theophylline, glutethimide, rifampicin
Skeletal antiresorptive agents: Bisphosphonates, denosumab, estrogens, raloxifene, calcitonin, plicamycin, colchicine overdose
Loop diuretics
PPIs and H2-blockers
Glucocorticoid therapy
Others:
Propylthiouracil (PTU)
Dobutamine
Calcium channel blockers
Strontium-89
Deferasirox
Bicarbonate therapy
Electroconvulsive therapy

often due to PTH deficiency or resistance. A large portion of non-PTH-related causes are due to vitamin D deficiency or resistance, with a wide variety of other less common causes. This section briefly

reviews the multiple causes of hypocalcemia, and gives several case illustrations of different causes.

## PTH-Mediated Hypocalcemia

### Hypoparathyroidism

By far the most common cause of hypoparathyroidism in adults is postsurgical hypoparathyroidism [7]. Postsurgical hypoparathyroidism occurs after neck surgery, but not only due to surgery targeting the parathyroid glands. The parathyroid glands may be adversely affected by compromised blood supply after manipulation during surgery on other neck structures, or by inadvertent removal. Postsurgical hypoparathyroidism usually results in hypocalcemia within 24–48 h after surgery, and is usually temporary. Different centers have reported different rates of symptomatic hypoparathyroidism after thyroid cancer surgery, ranging from 1 to 46 % of cases [8], whereas long-term postsurgical hypoparathyroidism is usually limited to less than 1–2 % of cases, depending on surgical expertise. The rate of post-thyroidectomy hypoparathyroidism increases with the stage of thyroid cancer, and is dependent on the extent of surgery, with about half of stage IV patients suffering from postsurgical hypoparathyroidism.

### Illustration: Case 1

A 29-year-old female was referred for post-thyroidectomy tetany. She had undergone surgery for a benign multinodular goiter, without evidence of malignancy at pathology review. The morning after surgery, her serum total calcium was decreased at 5.8 mg/dL (normal, 8.9–10.1), serum phosphorus mildly increased at 4.8 mg/dL (normal, 2.5–4.5), and serum creatinine normal at 0.9 mg/dL (normal, 0.8–1.3). Her serum 25-hydroxyvitamin D was normal at 38 ng/mL (optimal, 20–50 ng/mL). Her serum parathyroid hormone was undetectable at <6 pg/mL (normal, 15–65). Her serum magnesium was normal at 1.9 mg/dL (normal, 1.7–2.3 mg/dL). These findings indicate that postsurgical hypoparathyroidism was the cause of her hypocalcemia and hyperphosphatemia. Unfortunately about 75 %

of adults diagnosed with acquired hypoparathyroidism are postsurgical, with surgery sometimes being done for benign causes such as goiter or primary hyperparathyroidism, but more often for thyroid or other head or neck cancers.

Most patients with postsurgical hypoparathyroidism have transient hypoparathyroidism. Experience of the surgeon performing surgery generally predicts the incidence of postsurgical hypoparathyroidism. Immediate postoperative PTH levels may be useful in predicting which patients will develop permanent hypocalcemia due to postsurgical hypoparathyroidism [9].

Nonsurgical hypoparathyroidism may be due to deficiency or excess of serum magnesium [10, 11]. Hypomagnesemia usually causes hypoparathyroidism when serum magnesium is less than 1.0 mg/dL. Up to 11 % of hospitalized patients may have hypomagnesemia, while up to 9 % may have hypermagnesemia [12]. Hypomagnesemia may be due to gastrointestinal losses associated with vomiting related to excessive alcohol intake, chronic diarrhea, steatorrhea, malabsorption, or intestinal resection; renal tubular losses due to medications such as furosemide, aminoglycosides, cisplatin, cyclosporin, amphotericin B, pentamidine, tacrolimus, or proton pump inhibitors [13]; or rare genetic disorders such as Gitelman syndrome. Hypomagnesemia occurs frequently in critically ill patients, which contributes to the hypocalcemia frequently seen in intensive care unit patients. Hypermagnesemia may occur in the setting of late-stage chronic kidney disease in patients treated with magnesium antacids, enemas, or infusions, or acute renal failure associated with rhabdomyolysis or tumor lysis syndrome [14].

### Illustration: Case 2

A 48-year-old male was referred for possible hypoparathyroidism. His serum calcium was decreased at 6.7 mg/dL (normal, 8.9–10.1 mg/dL), with serum phosphorus increased at 5.5 mg/dL (normal, 2.5–4.5 mg/dL), and serum creatinine normal at 1.3 mg/dL (normal, 0.8–1.3 mg/dL). His serum 25-hydroxyvitamin D was normal at 45 ng/mL (optimal, 20–50 ng/mL). His serum PTH was decreased at 8 pg/mL (normal, 15–65 pg/mL). His

serum magnesium was very low at 0.8 mg/dL (normal, 1.7–2.3 mg/dL). These findings indicate that significant magnesium deficiency was the primary cause of his hypoparathyroidism leading to hypocalcemia and hyperphosphatemia. Further evaluation demonstrated renal tubular magnesium wasting due to previous use of outdated aminoglycoside antibiotics.

Primary intestinal hypomagnesemia results from a rare inherited disorder causing magnesium malabsorption leading to hypomagnesemia in early infancy. This condition is thought to primarily occur due to deficient intestinal magnesium absorption, but there may also be defects in renal magnesium reabsorption. Patients usually present with neurological symptoms, including tetany, muscle spasms, and seizures due to both hypomagnesemia and hypocalcemia associated with hypoparathyroidism. Lifelong high oral intake of magnesium supplements decreases symptoms and restores serum calcium levels to normal. Mutations in the *TRMP6* gene on chromosome 9 have been identified to cause this disorder [15, 16]. The TRMP6 protein is a member of the transient receptor membrane potential channel family that complexes to TRPM7, a calcium- and magnesium-permeable cation channel.

Other acquired causes of hypoparathyroidism are much rarer. Infiltration and destruction of the parathyroid glands by iron overload may occur in hemochromatosis, or thalassemia requiring multiple blood transfusions [17]. Copper overload occurring due to Wilson's disease may also result in hypoparathyroidism [18].

Hypoparathyroidism may result from metastases to the parathyroid glands in extremely rare circumstances [19]. External beam radiation therapy to the neck for treatment of malignant disease in this region, or radioactive iodine therapy for Graves' disease, may also rarely result in destruction of the parathyroid glands [20].

Inherited causes of hypoparathyroidism include autosomal dominant hypocalcemia (ADH), a condition in which there is a gain-of-function mutation in the *CaSR* [21]. This type of mutation changes the threshold of PTH secretion by parathyroid cells in response to circulating



ionized calcium, leading to low or inappropriately normal PTH secretion despite hypocalcemia. Most of the mutations reported to date affect the extracellular amino-terminal or transmembrane domains of the receptor. The mutant receptors may show both increased receptor sensitivity to calcium and increased maximal signal transduction capacity.

Since this activating mutation is also expressed in the CaSR on proximal renal tubular cells in the thick ascending limb of Henle, absolute or relatively increased 24-h urinary calcium excretion is a hallmark of the disorder. Most patients with ADH are asymptomatic and have mild hypocalcemia with significant hypercalciuria, but occasional patients may present with moderate or severe hypocalcemia. This form of CaSR-mediated hypoparathyroidism may cause increased risk of nephrocalcinosis compared to other forms of hypoparathyroidism. In one series, almost half of the patients evaluated had nephrocalcinosis associated with hypercalciuria [22]. Calcium supplementation must therefore be monitored carefully in this condition.

Occasional reports have described patients with CaSR gain-of-function mutations associated with a Bartter-like syndrome, suggesting that the CaSR may also play a role in sodium chloride regulation [23]. These patients present with hypocalcemia, hypercalciuria, and nephrocalcinosis, associated with hypokalemic alkalosis, renal salt wasting that may cause hypotension, hyperreninemic hyperaldosteronism, and increased urinary prostaglandin excretion. Extensive burns may lead to upregulation of the CaSR, with lower than normal serum calcium suppressing PTH secretion, resulting in hypocalcemia and hypoparathyroidism.

Autoimmune hypoparathyroidism is thought to be the second most common form of acquired hypoparathyroidism. Isolated autoimmune destruction of the parathyroid glands may occur, resulting in idiopathic hypoparathyroidism, or autoimmune destruction may occur in association with other autoimmune conditions as part of autosomal recessive autoimmune polyglandular endocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome [24]. This syndrome is

caused by mutations in the autoimmune regulator gene *AIRE*, which results in abnormal thymic expression of tissue antigens, generation of autoreactive T cells, ultimate loss of central tolerance to specific self-antigens, and the development of multiple autoimmune disorders [25]. Antibodies against the CaSR have been identified in some individuals with both idiopathic hypoparathyroidism or APECED syndrome [26, 27], but it is not yet clear if these antibodies are causative or simply markers of disease [28]. Idiopathic autoimmune hypoparathyroidism most often occurs in the teens or the young adulthood, but may occur at any age. APECED usually presents in childhood, and is characterized by chronic mucocutaneous candidiasis in addition to variable expression of endocrine and other autoimmune diseases. Variation in the clinical phenotype of individuals with identical mutations in the *AIRE* gene is incompletely understood, but this suggests that other genetic loci or environmental factors are important in the development of the phenotype.

Hypoparathyroidism may be diagnosed at birth or during childhood due to a variety of genetic mutations causing congenital syndromes, the most widely known being the DiGeorge (velocardiofacial) syndrome [29]. This disorder is caused by abnormal development of neural crest cells in the third and fourth branchial pouches. In 90 % of cases the syndrome is caused by heterozygous chromosomal deletion of the *TBX1* gene in the region of chromosome 22q11. Thirty-five genes have been identified in this region, so deletion of other genes, alone or in combination, could also cause this syndrome, but the *TBX1* gene is a major determinant of cardiac, thymus, and parathyroid cell phenotypes. A region on chromosome 10p (DiGeorge critical region II) has also been linked to the syndrome. DiGeorge syndrome is associated with distinctive facial abnormalities, cleft lip and/or palate, conotruncal cardiac anomalies, and mild-to-moderate immune deficiency. Hypocalcemia due to hypoparathyroidism has been reported in 17–60 % of affected children [30]. DiGeorge syndrome is estimated to occur in as many as 1:2,000–1:3,000 births, with the incidence rate of new mutations estimated at 1:4,000–1:6,000.

**Table 21.3** Characteristics of pseudohypoparathyroidism subtypes

Type	Gs $\alpha$ activity	AHO	PTH resistance	Urinary cAMP response	Multiple hormone resistance	Molecular defect
1a	Reduced	Yes	Yes	Reduced	Yes	Heterozygous mutations in <i>GNAS</i>
Pseudo-PHP	Reduced	Yes	No	Normal	No	Heterozygous mutation in <i>GNAS</i>
1b	Normal	No	Kidney	Reduced	No	Imprinting defect in <i>GNAS</i>
1c	Normal	No	Yes	Reduced	Yes	Unknown
2	Normal	No	Kidney	Normal	No	Unknown

*AHO* indicates Albright's hereditary osteodystrophy, *cAMP* cyclic adenosine monophosphate, *PTH* parathyroid hormone

Because the clinical phenotype varies, findings may be subtle and therefore overlooked, and mild hypocalcemia may be easily missed. In one study of adults with chromosome 22q11.2 deletion, about half were hypocalcemic, with a median age of presentation of 25 years, and a maximum age of diagnosis of up to 48 years [31]. This disorder may rarely be diagnosed for the first time as late as the mid-60s, with late onset of mild hypocalcemia, and is not infrequently diagnosed in an affected parent in the 20s or 30s after birth of an affected child.

Finally, a variety of other rare genetic or inherited disorders may cause hypocalcemia that is recognized in infancy or childhood. Familial isolated hypoparathyroidism due to autosomal recessive or dominant mutations in the *pre-proPTH* gene on chromosome 11p15 [32, 33], or parathyroid gland dysgenesis due to mutations in various transcription factors regulating parathyroid gland development such as *GCMB* (glial cells missing B) [34] or *GCM2* (glial cells missing 2) [35], *GATA3* [36, 37], or Sry-box 3 (*SOX3*) [38], is thought to be very rare. Autosomal dominant hypoparathyroidism associated with deafness and renal anomalies has been linked to mutations in the *GATA3* gene on chromosome 10p14-10-pter [36, 37]. Hypoparathyroidism has been very rarely associated with X-linked recessive mutations on Xq26-27, leading to disruption of *SOX3* transcription [38]. The syndrome of autosomal recessive hypoparathyroidism, growth and mental retardation, and dysmorphism due to mutations in the *TBCE* gene on chromosome 1q42-q43 is another very rare cause of hypoparathyroidism [39]. Hypoparathyroidism with

metabolic disturbances and congenital anomalies has been associated with rare maternal mitochondrial gene defects [40, 41].

### PTH Resistance

Pseudohypoparathyroidism (PHP) is a complex disorder with several recognized subtypes, characterized biochemically by hypocalcemia, hyperphosphatemia, and hyperparathyroidism due to tissue unresponsiveness to PTH [42] (Table 21.3). Most often hypocalcemia is not present at birth, and typically develops during childhood. The previous gold standard for diagnosis of PHP was the Ellsworth–Howard test, in which bovine PTH was infused to determine if urinary cyclic AMP increased normally. In most forms of PHP, urinary cyclic AMP does not increase as expected. This test is rarely performed today due to lack of bovine PTH, and the diagnosis is often based on the constellation of biochemical findings, family history when present, and genetic analysis.

PHP is further classified as types 1a, pseudo-PHP, 1b, 1c, or 2. In PHP type 1a, the most common subtype, loss-of-function mutations in the coding region of the maternally inherited *GNAS* gene encoding the Gs $\alpha$  subunit of G proteins, causes the disorder, with resultant 50 % loss of Gs $\alpha$  protein expression [43]. PHP type 1a patients have PTH resistance at the renal tubule, resulting in a blunted phosphaturic and cAMP response to PTH. This blunted response is due to lack of normal signaling by the PTH receptor due to reduced stimulatory G protein expression.

PHP type 1a is characterized by Albright's hereditary osteodystrophy (AHO), which includes obesity, round facies, mild mental retardation, and

a skeletal phenotype involving short stature, brachydactyly of hands and/or feet, and heterotopic ossifications in subcutaneous tissues. This disorder is frequently associated with multiple hormone resistance involving thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), calcitonin, and/or growth hormone-releasing hormone (GHRH).

Patients with PHP type 1a have renal tubule PTH resistance because they inherit a mutated maternally imprinted *GNAS* allele. *GNAS* alleles undergo differential imprinting in mothers and fathers, with tissue-specific expression of alleles in offspring. Only the maternal allele is expressed in the kidney and in the relevant endocrine organs associated with hormone resistance in this form of the disorder, but the rest of the body expresses both maternal and paternal alleles. An affected allele in other body tissues leads to haploinsufficiency and AHO expression, but PTH resistance occurs only in the tissues expressing the maternal allele.

Patients with paternally inherited *GNAS* mutations who have AHO without renal or endocrine gland resistance are designated as having pseudo-PHP. Patients with pseudo-PHP have a normal urinary cAMP response to PTH, unlike PHP type 1a patients. Patients with both PHP type 1a or pseudo-PHP may occur in the same kindred. In some cases both forms are found in the same generation, but more often the two forms are found in different generations.

PHP type 1b patients lack typical features of AHO, but may have mild brachydactyly [44]. Levels of  $Gs\alpha$  in accessible tissues are normal, but patients have renal tubular PTH resistance without resistance to other hormones, although some may have mildly increased TSH levels. Skeletal manifestations are similar to those seen in patients with hyperparathyroidism, with bone loss or changes of osteitis fibrosa cystica. Most cases are due to switching of the maternal *GNAS* allele to a paternal pattern of methylation, caused by microdeletions in the *STX16* gene located 220 kB centromeric from *GNAS* exon 1A, or deletions removing the differentially methylated region involving exon NESP55 or exons 3 and 4 of the antisense transcript [45]. In both situations, inheritance of a mutation from a female, or spon-

taneous mutation of a maternally derived allele, removes the maternal *GNAS* epigenotype, leading to transcriptional silencing of the  $Gs\alpha$  promoter in imprinted tissues, with little or no expression of either *GNAS* allele in these tissues.

Patients with PHP type 1c have normal  $Gs\alpha$  activity and lack identifiable mutations in *GNAS*, and are thought to represent a variant of PHP type 1a. PHP type 2 patients have normal cAMP production in response to administered PTH, but lack a phosphaturic effect. Little is known about the mutations involved, but because the biochemical picture is similar to that of severe vitamin D deficiency, it may be that most, if not all, cases of PHP type 2 are due to unsuspected vitamin D deficiency.

PTH stimulates the proximal tubule to decrease phosphate reabsorption and increase calcium reabsorption in the distal tubule. In patients with PHP type 1a, the distal tubule phosphaturic effect is blunted and there is no hypercalciuric effect, so these patients do not form kidney stones as might be expected. Calcium may therefore be supplemented to a greater level than in other causes of hypoparathyroidism without contributing to calcium nephrolithiasis [46].

Hypomagnesemia also causes PTH resistance, and there is often a lag time to normalization of serum calcium levels despite a normal or an increased PTH level after magnesium repletion [14].

## Vitamin D-Related Hypocalcemia

Patients with vitamin D deficiency or resistance often develop hypocalcemia. Nutritional vitamin D deficiency may be the most common cause of hypocalcemia throughout the world, resulting from inadequate intake or lack of sunlight exposure [47]. Intestinal malabsorption of vitamin D from many causes may also lead to hypocalcemia. Rare cases of vitamin D resistance, either due to  $1\alpha$ -hydroxylase deficiency or vitamin D receptor mutations, typically present with hypocalcemia. Consequences of hypocalcemia associated with vitamin D deficiency may be severe, including increased risk of hip fracture [48].

## Vitamin D Deficiency

Vitamin D2 (ergocalciferol) is normally obtained from plant sources or supplements, and vitamin D3 (cholecalciferol) from skin sunlight exposure or supplements. Both forms are transported in the circulation to the liver by vitamin D-binding protein, where they are converted by 25-hydroxylase to 25-hydroxyvitamin D, and then in a smaller amount to the kidneys, where they are 1 $\alpha$ -hydroxylated to 1,25-dihydroxyvitamin D. Serum 1,25-dihydroxyvitamin D is the biologically active form of vitamin D in the body because of its 1,000-fold higher affinity for the vitamin D receptor than 25-hydroxyvitamin D, and this form normally stimulates the intestine to actively transport calcium and phosphorus from the lumen into the bloodstream by upregulating intestinal transport proteins, particularly when calcium or phosphorus intake is decreased [49]. Serum 1,25-dihydroxyvitamin D also directly suppresses PTH transcription in parathyroid cells, leading to decreased PTH secretion, as well as stimulating osteoclast and osteoblast recruitment and activation in the skeleton. This form of vitamin D feeds back to suppress its own production by renal 1 $\alpha$ -hydroxylase, and stimulates 24-hydroxylase to increase its own metabolism. Because increased serum PTH, decreased serum calcium, or increased serum phosphorus all normally independently upregulate renal 1 $\alpha$ -hydroxylase, hypoparathyroidism leads to reduced renal 1 $\alpha$ -hydroxylase activity and decreased 1,25-dihydroxyvitamin D production if serum calcium and phosphorus do not change to accommodate the decreased PTH level.

### Illustration: Case 3

A 58-year-old female was seen in hospital after falling at home and sustaining a left hip fracture. Her serum calcium before fracture repair was 7.6 mg/dL (normal, 8.9–10.1 mg/dL), with serum phosphorus 2.3 mg/dL (normal, 2.5–4.5 mg/dL), with her serum creatinine normal at 1.1 mg/dL (normal, 0.6–1.1 mg/dL). Her serum 25-hydroxyvitamin D was very low at 6.6 ng/mL (optimal, 20–50 ng/mL). Her serum PTH was increased at 82 pg/mL (normal, 15–65 pg/mL). Her serum magnesium was normal at 2.2 mg/dL

(normal, 1.7–2.3 mg/dL). Her findings indicate that she had significant vitamin D deficiency as the cause of her hypocalcemia and mild hypophosphatemia. Her profound vitamin D deficiency was attributed to lack of sunlight exposure and lack of dietary or supplemental intake of vitamin D. She had been avoiding sunlight to minimize her risk of skin cancer. Vitamin D3 replacement with 50,000 U twice weekly was started after hip surgery for 2 months.

Any cause of vitamin D deficiency may lead to both hypocalcemia and hypophosphatemia, triggering an increase in PTH that upregulates renal 1 $\alpha$ -hydroxylase. Persistent stimulation of PTH secretion by any cause often leads to increased serum alkaline phosphatase and bone loss over time. If vitamin D deficiency is severe and chronic, this may ultimately lead to excessive production of unmineralized collagenous and noncollagenous matrix in the skeleton, leading to osteomalacia in adults, or rickets in children.

It has become appreciated that vitamin D deficiency is common in community-dwelling adults in most countries [50], as well as in hospitalized patients [51], but the prevalence estimate depends on how vitamin D deficiency is defined. Most experts consider serum 25-hydroxyvitamin D to be the best marker of nutritional vitamin D intake currently available, with levels below 10 ng/mL (25 nmol/L) considered deficient because of the increased likelihood of osteomalacia or rickets at this level [52]. Optimal levels associated with nutritional adequacy continue to be debated, with most bone specialists recommending 30 ng/mL (75 nmol/L) for treatment of osteoporosis or metabolic bone disease. The 2011 US Institute of Medicine report concluded that 20 ng/mL (50 nmol/L) was adequate for maintenance of skeletal health in the general population, and emphasized that optimal vitamin D levels have not yet been established for most human diseases [53]. In light of the current controversy regarding vitamin D adequacy and optimal levels, vitamin D insufficiency is most often defined as levels between 10 and 20 ng/mL (25–50 nmol/L).

Excessive supplementation with vitamin D by patients is increasingly common, frequently leading to hypercalciuria, but vitamin D toxicity man-

ifested by hypercalcemia remains uncommon. Most bone specialists regard serum 25-hydroxyvitamin D levels above 80 ng/mL (200 nmol/L) with concern, but it is uncommon to see hypercalcemia unless serum 25-hydroxyvitamin D is greater than 150 ng/mL (375 nmol/L).

Any cause that disrupts vitamin D absorption, synthesis, transport, interaction with vitamin D receptors in target tissues, or metabolism may lead to a decrease in vitamin D actions [47]. Inadequate sunlight exposure, especially in the elderly, or those with hyperpigmented skin or using high-grade sun block to prevent sunburn, may develop vitamin D deficiency. Any cause of malnutrition, intestinal malabsorption, chronic liver disease, or mid- or late-stage chronic kidney disease may lead to inadequate vitamin D absorption or production. Drugs that upregulate cytochrome P450 enzymes that metabolize vitamin D, such as anticonvulsants, including phenytoin, phenobarbital, carbamazepine, or valproate, may lead to vitamin D deficiency if sunlight exposure or dietary or supplemental intake is not sufficient to compensate for increased metabolism [54].

Rare mutations in the CYP27B1 gene affecting the activity of renal  $1\alpha$ -hydroxylase activity give rise to pseudovitamin D deficiency rickets, previously known as vitamin D-dependent rickets type 1 (VDDR1) [55, 56]. This condition results in partial or complete deficiency of the  $1\alpha$ -hydroxylase enzyme, leading to very low levels of 1,25-dihydroxyvitamin D production, with significant hypocalcemia and hypophosphatemia. This condition is diagnosed shortly after birth or in infancy with tetany, seizures, rickets, and failure to thrive. Nutritional vitamin D deficiency causes decreased serum calcium, phosphorus, and 25-hydroxyvitamin D levels, but serum 1,25-dihydroxyvitamin D levels typically remain normal until serum 25-hydroxyvitamin D levels fall to less than 4 ng/mL (10 nmol/L). In this situation, lack of substrate availability leads to a decrease in serum 1,25-dihydroxyvitamin D. In pseudovitamin D deficiency rickets, lack of functional  $1\alpha$ -hydroxylase leads to low serum calcium and phosphorus, increased total and bone alkaline phosphatase, normal 25-hydroxyvitamin D, and very low or undetectable 1,25-dihydroxyvitamin D levels.

### Vitamin D-Resistant Rickets

Hereditary vitamin D-resistance rickets is a rare autosomal recessive genetic disorder previously known as VDDR type 2 [57]. This disorder is caused by a mutation in the vitamin D receptor that leads to resistance to the action of 1,25-dihydroxyvitamin D. Mutations have been reported in the ligand-binding domain, DNA-binding domain, and other domains. Resistance to 1,25-dihydroxyvitamin D may be partial or complete. Affected children typically present before age 2 years, but occasionally as late as their teens, similar to children with pseudovitamin D deficiency rickets [58], with tetany, seizures, rickets, and failure to thrive. Laboratory assessment shows hypocalcemia, hypophosphatemia, increased alkaline phosphatase, normal 25-hydroxyvitamin D, and increased 1,25-dihydroxyvitamin D. Hyperparathyroidism resulting from the hypocalcemia stimulates renal  $1\alpha$ -hydroxylase production of 1,25-dihydroxyvitamin D. Increased serum 1,25-dihydroxyvitamin D is the main biochemical feature distinguishing this disorder from pseudovitamin D deficiency rickets. Patients have partial or total scalp alopecia in two-thirds of the kindreds reported. The level of hypocalcemia is variable between kindreds as well. Patients do not respond to usual replacement doses of vitamin D or calcium, but may respond to pharmacological doses of vitamin D in some cases, depending on residual vitamin D receptor activity. Those with no vitamin D receptor activity usually require treatment with intravenous calcium and/or high-dose oral calcium.

### Other Causes of Hypocalcemia

A variety of heterogeneous causes of hypocalcemia exist beyond those commonly recognized to be due to hypoparathyroidism or vitamin D deficiency or resistance.

Hyperphosphatemia of any cause, but commonly due to later stage chronic kidney disease, may reduce serum calcium by complexing to calcium in the circulation and causing soft tissue deposition of calcium phosphate complexes. Renal failure is associated with hyperphosphatemia and

decreased  $1\alpha$ -hydroxylase activity, leading to decreased 1,25-dihydroxyvitamin D production. A variety of medications may cause hyperphosphatemia if taken in excessive amounts, including phosphate binders, phosphate-containing laxatives or enemas, or intravenous phosphorus given to lower serum calcium. Tumor lysis syndrome and rhabdomyolysis may result in acute hyperphosphatemia and lead to acute hypocalcemia.

Transfusions of citrated blood products, usually in large quantities, may cause acute hypocalcemia due to the formation of calcium citrate complexes in the serum. Acute pancreatitis releases lipase into surrounding tissue fluids, which may lead to increased free fatty acids that saponify calcium, resulting in significant hypocalcemia. Excessive uptake of calcium by bone that overwhelms homeostatic mechanisms in place to maintain normal serum calcium will cause hypocalcemia, as seen with “hungry bone” syndrome after surgical cure of severe, long-standing hyperparathyroidism. Older age, higher preoperative serum alkaline phosphatase levels, and larger weight of resected adenoma all predict a higher risk of “hungry bone” syndrome [59]. Rarely, extensive osteoblastic metastases may cause hypocalcemia because of rapid uptake and formation of new bone. Critical illness is often associated with hypocalcemia because of multiple concurrent causes that may be present [60].

A variety of medications may directly cause hypocalcemia by a variety of mechanisms (Table 21.3). Pseudohypocalcemia may occur within several hours of administration of certain gadolinium-containing contrast agents for magnetic resonance imaging studies [61]. In this situation, spurious critical hypocalcemia of less than 6.0 mg/dL may be found because certain gadolinium agents, but not all, interfere with calcium measurement in certain colorimetric assays. In this case, rechecking serum calcium by a different assay method will usually clarify the diagnosis. Patients reported to have critical hypocalcemia in this setting usually remain asymptomatic, which should raise suspicion regarding the accuracy of the serum calcium level.

With the increasing recognition and treatment of osteoporosis, many patients are treated with

antiresorptive agents including oral and intravenous bisphosphonates, denosumab, or raloxifene that may precipitate hypocalcemia [62]. It is prudent to make sure that such patients are treated with adequate vitamin D and calcium before treating these patients to prevent hypocalcemia.

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## Laboratory Tests and Interpretation

Evaluation of hypocalcemia depends heavily on laboratory studies available to the clinician. Initial laboratory testing should involve measurement of serum total calcium, albumin for calculating albumin-corrected serum calcium, ionized calcium if available, magnesium, PTH, and 25-hydroxyvitamin D levels. Serum phosphorus and creatinine should be measured also, as interpretation of the other values is often difficult without serum phosphorus or creatinine.

Serum 25-hydroxyvitamin D is generally most reliably measured by tandem mass spectroscopy, but this expensive technique is not available in many laboratories. Most clinicians consider serum 25-hydroxyvitamin D less than 10 ng/mL (25 nmol/L) to be deficient because of the increased likelihood of osteomalacia [52]. The Institute of Medicine considers 20 ng/mL (50 nmol/L) an adequate level for skeletal purposes in healthy adults [53]. Serum 25-hydroxyvitamin D between 10 and 20 ng/mL (25–50 nmol/L) is considered by most bone specialists to be insufficient. The upper limit of normal for serum 25-hydroxyvitamin D is considered to be 50 ng/mL (75 nmol/L) by many bone specialists because of the hypercalciuria that may occur above this level. Vitamin D toxicity, with associated hypercalcemia, typically does not occur unless serum 25-hydroxyvitamin D is greater than 150 ng/mL (375 nmol/L), but may rarely occur when above 80 ng/mL (200 nmol/L).

Measurement of intact PTH by a reliable assay will detect inappropriately low, low-normal, or undetectable values in hypoparathyroid patients. There is less variability in measurement of PTH than 25-hydroxyvitamin D. Serum magnesium deficiency or excess may both limit secretion of PTH [11, 12], so patients with apparent

hypoparathyroidism with low serum calcium, increased serum phosphorus, normal creatinine, normal 25-hydroxyvitamin D, and low PTH should always have their serum magnesium checked. Patients with hypoparathyroidism usually have low serum calcium, increased serum phosphorus, normal creatinine, normal 25-hydroxyvitamin D, and low-to-undetectable PTH. Patients with pseudohypoparathyroidism typically have low serum calcium, increased serum phosphorus, normal creatinine, normal 25-hydroxyvitamin D, and increased PTH. Patients with vitamin D deficiency usually have low serum calcium and phosphorus, normal creatinine, and increased PTH.

Measurement of 24-h urine calcium or magnesium may be very important in sorting out the cause of hypocalcemia. Increased 24-h urine calcium may suggest idiopathic hypercalciuria in the untreated patient, but is likely due to overtreatment with calcium or vitamin D supplementation in treated hypocalcemic patients. Markedly increased 24-h urinary calcium and asymptomatic mildly decreased serum calcium may be due to autosomal dominant hypocalcemia. Untreated hypocalcemic patients usually have decreased or low-normal 24-h urine calcium. Increased 24-h urine magnesium in the setting of hypomagnesemia strongly suggests renal tubular magnesium wasting, rather than gastrointestinal loss of magnesium.

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## Management

Treatment of hypocalcemia is intended primarily to improve or eliminate symptoms, reverse skeletal demineralization to the degree it is present, heal osteomalacia if present, maintain acceptable serum total or ionized calcium, and avoid hypercalciuria (24-h urine calcium >300 mg), renal dysfunction, kidney stones, and nephrocalcinosis [63]. Patients who have need for urgent treatment due to symptoms such as tetany, seizures, laryngospasm, bronchospasm, cardiac rhythm disturbances, or altered mental status, or severe hypocalcemia, require intravenous calcium, usually given as calcium gluconate. Typically ten 10-mL ampules of calcium gluconate, with

93 mg elemental calcium per ampule, are added to 900 mL of 5 % dextrose, and 10 mL infused slowly over 10 min to improve symptoms, with repeat infusion given once or twice more as needed. A maintenance infusion is then typically begun at 10–100 mL/h to control symptoms and improve serum calcium to the lower end of the normal range at around 8.5 mg/dL (2.12 mmol/L), with ionized calcium of around 4 mg/dL (1.0 mmol/L). The infusion rate can be calculated to give 0.3–1.0 mg elemental calcium/kg/h.

After stabilization of the patient, an oral regimen is started, providing the patient with at least 500 mg three to four times a day. The calcium gluconate infusion is gradually tapered as serum calcium approaches the target level, symptoms improve, and oral calcium supplements are tolerated.

Management of chronic hypocalcemia usually involves oral calcium and vitamin D supplementation, sometimes with thiazide-type diuretics or magnesium supplementation. If serum magnesium levels are decreased, magnesium total body deficits are usually very large, but poorly reflected by the serum magnesium level, because magnesium is mostly located intracellularly. Supplementation with magnesium usually takes months to fully replete body stores. As serum magnesium is gradually repleted, serum calcium and PTH levels return toward normal.

Oral calcium supplements of any type will restore serum calcium toward normal. In general, calcium carbonate or calcium citrate are used most commonly because they are widely available and relatively inexpensive. Calcium carbonate is 40 % calcium by weight, and calcium citrate 21 % calcium by weight. Calcium supplements are usually given in divided doses each day, typically between two and four times a day, with dosing given with meals to enhance absorption. Starting doses are usually 500–1,000 mg elemental calcium two or three times each day, and titrated upward as needed based on the tolerability, compliance, and clinical target. If calcium supplementation alone is insufficient to achieve serum calcium of 8.0–8.5 mg/dL (2.0–2.13 mmol/L), active vitamin D supplementation is usually started. If renal function is normal,

vitamin D2 (ergocalciferol) or D3 (cholecalciferol) may be started at 1,000–4,000 International Units each day, or alternatively, 50,000 International Units once weekly to several times a week as needed, depending on intestinal absorption efficiency. Severe hypoparathyroidism or PHP typically requires higher doses of vitamin D. Care must be taken with these forms of vitamin D, however, as their half-life is prolonged due to storage in body fat, and toxic serum levels of 25-hydroxyvitamin D may take 6–9 months to clear after supplementation is stopped. Because of concerns regarding toxicity, calcitriol (1,25-dihydroxyvitamin D) 0.25 mcg once or twice a day is often started in place of vitamin D2 or D3 in the USA, whereas alfacalcidol (1 $\alpha$ -hydroxyvitamin D) in low doses is used in Europe. The half-life of these forms of vitamin D is on the order of 1–3 days, so improvement in absorption or offset of action occurs more rapidly. Commercial parenteral vitamin D is no longer available in the USA, but some hospital-compounding pharmacies produce intravenous vitamin D3 based on clinical need.

Patients who develop hypercalciuria while on calcium and vitamin D supplementation, or who are unable to achieve or maintain serum calcium at or near their target range, may require addition of a thiazide-type diuretic to reduce urinary calcium loss. Doses of hydrochlorothiazide or chlorthalidone of 12.5–25 mg each day may be beneficial, but some patients may require as much as 50 or 100 mg to decrease their 24-h urine calcium to less than 300 mg.

Once- or twice-daily injections of PTH 1-34 (teriparatide or other) have been used off-label in short-term trials to normalize serum and urine calcium and phosphorus in patients with hypoparathyroidism [64, 65]. This therapy has not been approved by the FDA for treatment of hypoparathyroidism. A pivotal 6-month phase III clinical trial with PTH 1-84 (Natpara) has recently been completed, with FDA evaluation for approval for treatment of hypoparathyroidism pending. Parathyroid allograft transplants have been used in a few individuals who either previously or simultaneously have undergone renal transplantation [66, 67]. Advances in stem cell

technology may some day permit stem cells to be used to create new parathyroid tissue in patients where it is lacking.

Patients with pseudovitamin D deficiency rickets (VDDR1) respond to physiologic doses of 1,25-dihydroxyvitamin D3 and calcium, and require lifelong therapy. Patients with hereditary vitamin D-resistant rickets (vitamin D-dependent rickets type 2) are challenging to manage, because pharmacologic doses of 1,25-dihydroxyvitamin D3 are usually required to overcome resistance. Calcium supplements of up to 3,000 mg elemental calcium may be required. Therapy is continued until undermineralized bones are mineralized, typically within 2–6 months. Close follow-up is necessary to monitor parameters of calcium and mineral metabolism and clinical signs and symptoms. Some cases have failed to respond to this therapy despite 1,25-dihydroxyvitamin D3 levels more than 100 times normal. Long-term calcium infusions in combination with high-dose oral calcium supplements have been used successfully in this situation.

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## Epidemiology

Primary hyperparathyroidism is not a rare disease. It is more common in subjects over 50 years of age and in postmenopausal women. In addition, the prevalence of primary hyperparathyroidism is about 0.78 % for patients evaluated in reference centers, in both the public and private institutions [1].

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## Etiology

The solitary parathyroid adenoma appears in 85–90 % of the cases [2, 3]. Hyperfunction in several parathyroid glands associated with hyperplasia and multiple adenomas occurs in most other cases [4]. In this context, it is important to mention that the disorder in multiple glands represents the most usual finding in subjects who have the primary hyperparathyroidism (PHPT) familial

syndromes, corresponding to about 10 % of cases [3]. On the other hand, parathyroid carcinoma occurs rarely, accounting for 0.7 % of all cases [2]. Furthermore familial PHPT is related to several pathological entities, such as multiple endocrine neoplasia type 1 (MEN 1) and type 2 (MEN 2), familial hypocalciuric hypercalcemia, familial hypercalciuric hypercalcemia, and the jaw tumor hyperparathyroidism syndrome in familial isolated hyperparathyroidism [5] (Table 22.1).

MEN1 can be considered a rare cause of PHPT, the incidence of MEN1 being about 2–4 % of PHPT cases. However, PHPT is the most common endocrinopathy in the MEN1 syndrome: it is found in almost 100 % of the patients over 50 years of age and constitutes the first sign of the disease in most carriers in their twenties [5]. The diagnosis of PHPT in young adults should therefore include the search for MEN1. The search for MEN1 should also be conducted in the immediate family. The prevalence of PHPT in MEN-2 is lower than in MEN-1 and is found in 20–30 % of cases. Furthermore, the majority of patients with PHPT present clinical manifestations that are more discrete than the clinical signs demonstrated by MEN-1 carriers [6].

The jaw tumor hyperparathyroidism syndrome is a rare disease. Evidence shows that bone tumors of the jaw related to PHPT can be outlined [7]. Parathyroid cancer has been also detected in more than 15 % of cases [7].

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**Table 22.1** Familial primary hyperparathyroidism

Multiple endocrine neoplasia type 1 (MEN 1)
Multiple endocrine neoplasia type 2 (MEN 2)
Familial hypocalciuric hypercalcemia
Familial hypercalciuric hypercalcemia
Hyperparathyroidism—jaw tumor syndrome
Familial isolated hyperparathyroidism

Adapted from ref. [5]

## Diagnosis

In familial isolated hyperparathyroidism, cases of PHPT are diagnosed in the immediate family in the absence of other endocrinopathies; this characterizes the phenotype as a hidden syndrome, such as MEN-1 and MEN-2 [4].

Hypercalcemia and an increase in PTH levels constitute the biochemical markers of PHPT. In normal conditions of hypercalcemia there is an inhibition of the parathyroid glands. This inhibition is translated by low levels of PTH [3].

The majority of patients with PHPT present slightly increased levels of PTH, but up to 10 % of the cases can exhibit normal to upper normal levels of PTH [8, 9]. Nevertheless, these levels are inappropriately high because of the hypercalcemia. Hypercalcemia is found in most of the cases of PHPT, but one has to consider the possibility of fluctuations in the levels of serum calcium, which could explain the normal levels of calcemia [8].

Diagnosis includes the evaluation of serum concentrations for calcium, phosphorus, albumin, alkaline phosphatase, intact PTH, 25 (OH)-D vitamin, and renal function [8, 9]. 24-h urinary calcium and the serum levels of creatinine must be evaluated in order to rule out the possibility of familial hypocalciuric hypercalcemia [10, 11].

About 40 % of serum calcium is linked to albumin. Serum levels must be adjusted according to the following equation: corrected calcium = serum calcium (mg/dL) +  $[0.8 \times (4 - \text{serum albumin})]$ . The measurement of the ionized calcium can be useful in specific cases, such as subjects with hyperalbuminemia, thrombocytosis, Waldenstrom's macroglobulinemia, and myeloma, since in these subjects there is hypercalcemia with normal ionized serum calcium (artifactual hypercalcemia) [10, 12].

In a retrospective cohort with 6,982 subjects, the serum ionized and total calcium were compared in patients with hypercalcemia. PTH-dependent hypercalcemia was set as total serum calcium (corrected by albumin) equal to or greater than 10.2 mg/dL or ionized calcium (technique of specific ion electrode) equal to or greater than 1.32 mmol/L with the PTH > 5 pmol/L (35 pg/mL; reference values 0.9–9 pmol/L). Among these subjects, 343 had high ionized calcium and 156 (45 %) had high total calcium. In a second cohort with 203 subjects, 143 presented histologically confirmed PHPT: high ionized serum calcium was present in 141 cases (98 %) and, lastly, increased total serum calcium in 108 (76 %), demonstrating a greater diagnostic accuracy when ionized serum calcium was used [13].

A cohort study, based on the population of Tayside in Scotland, used the following criteria to diagnose primary hyperparathyroidism: (1) serum calcium corrected for albumin > 10.22 mg/dL (reference values: 8.4–10.22 mg/dL) on at least two occasions, with serum PTH > 13.5 ng/L (reference values: 4.5–31.05 ng/L), or (2) serum calcium corrected for serum albumin > 10.22 mg/dL on one occasion with serum PTH > 31.05 ng/L [14]. These values of serum PTH correspond to 20 pg/mL for assays with reference values between 10 and 65 pg/mL.

The causes of secondary hyperparathyroidism that can increase the serum levels of parathormone, such as the use of thiazide diuretics [9] and lithium, deficiency of vitamin D, and the use of bisphosphonates, must be excluded. Concerning tertiary hyperparathyroidism due to renal failure, genetic causes such as familial hypocalciuric hypercalcemia also need to be sought. The finding of normal levels for calcium corrected by albumin and associated with high serum PTH in the absence of other causes is compatible with normocalcemic PHPT.

Serum PTH and the biochemical markers of the bone remodeling are significantly higher in patients with severe disease. These patients frequently have vitamin D deficiency and easier localization of the parathyroid lesion than asymptomatic patients [2].

The levels of serum phosphorus are usually found to be in the lower normal range. Specific

markers of bone modeling (osteocalcin and alkaline phosphatase osteo-specific) or markers of boneresorption (deoxypyridinoline, N-telopeptide, and C-telopeptide) seem to remain either in the high-normal range or slightly above reference values. Hypercalciuria is found in around 30 % of asymptomatic patients, in 50 % of patients with active urolithiasis, and in 40 % with osteitis fibrosa cystica [2, 9]. Patients with severe PHPT have moderate levels of serum calcium and lower levels of serum phosphorus as compared to asymptomatic subjects ( $14.0 \pm 0.7$  vs.  $10.9 \pm 0.4$  mg/dL;  $p < 0.001$  and  $2.0 \pm 0.5$  vs.  $296 \pm 0.2$  mg/dL;  $p < 0.01$ , respectively). In the serum levels of intact PTH, there are greater differences:  $1,820 \pm 349$  vs.  $133 \pm 29$  pg/mL;  $p < 0.001$  [15].

Serum PTH and the biochemical biomarkers of the bone remodeling are significantly higher in the patients with tevere disease, who frequently present vitamin D deficiency and easier localization of the parathyroid lesion than asymptomatic patients [16].

### Differential Diagnosis

PHPT needs to be differentiated from other causes of hypercalcemia (Table 22.2), as well as from diseases that can cause osteoporosis, nephrolithiasis, nefrocalcinosis, and hypophosphatemia. PHPT and neoplasia correspond to 90 % of hypercalcemia cases. Data from the literature

shows that 50–60 % of outpatients with hypercalcemia are carriers of the PHPT and about 31 % present neoplasia [18].

Hypercalcemia with very low or undetectable PTH plasma levels can be found when the disease is malignant and, in this case, the PTHrp is responsible for the increase in calcium [12]. Several laboratory characteristics associated with malignancy are similar to those of PHPT, such as hypercalcemia, hypophosphatemia, hypercalciuria, and hyperphosphaturia and an increase in the nephrogenic cyclic AMP [19]. However, the difference between primary HPT and the malignant disease with hypercalcemia can be identified without difficulty, based on the clinical history of the patient. The hypercalcemia symptoms of PHPT are manifested over months or years, while in malignancy these symptoms are manifested within weeks and are secondary to the underlying malignant disease. Thus, hypercalcemia in malignant disease is readily revealed and is frequently associated with a survival of about 6 months. Other related symptoms are anemia and weight loss. In general, when hypercalcemia is found, malignancy is clinically revealed by imaging techniques or bone metastasis presented by the patient. In addition to these parameters, persistent hypercalcemia of early onset suggests malignancy, whilst a mild hypercalcemia lasting for more than 6 months is more likely to be caused by PHPT.

The definitive differential diagnosis is performed by means of serum PTH measurement.

**Table 22.2** Differential diagnosis of hypercalcemia

1) Malignancies	Solid tumors Humoral hypercalcemia (carcinomas) Squamous lung, esophagus	Solid tumors Osteolytic hypercalcemia (breast, lung)	Hematologic malignancies (lymphoma, leukemia, multiple myeloma)	Ectopic production of PTH (thyroid carcinoma, ovarian, lung oat cells)
2) PTH dependent	NEM	PHPT: a) Adenoma b) Carcinoma c) Hyperplasia	Familial hypercalciuric hypercalcemia (FHH)	Treatment with lithium
3) Related to vitamin D	Idiopathic familial hypercalcemia	Granulomatous diseases	Vitamin D intoxication	–
4) Other causes	Milk-alkali syndrome, aluminum intoxication	Endocrine diseases (hyperthyroidism, pheochromocytoma, adrenal insufficiency)	Advanced chronic disease of the liver/ kidney	Drugs: Thiazide Theophylline Beryllium

Adapted from refs. [17, 18]

In PHPT, when PTH is increased or within normality the condition may be regarded as PTH-dependent hypercalcemia, but is frequently suppressed in malignant disease, which is independent of PTH [12]. In rare cases, PTH can be increased in malignancy due to ectopic production or when parathyroid carcinoma is the cause of the hypercalcemia [20].

Another differential diagnosis that should always be demanded is that of familial hypocalciuric hypercalcemia, which is characterized by a genetic defect in the calcium receptors in the parathyroid glands and kidneys, inherited as a dominant autosomal disorder [5]. The hypercalcemia is mild and followed by hyperphosphatemia, and levels of PTH are normal or slightly increased. The most pronounced laboratory finding is hypocalciuria, which suggests increased tubular resorption of calcium. This diagnosis is considered in young asymptomatic patients that present (1) levels of serum calcium with a slight-to-moderate increase, (2) hypocalciuria, (3) a familial history of hypercalcemia, and (4) a rate of calcium/creatinine clearance of less than 0.01 [17].

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## Normocalcemic Hyperparathyroidism

Patients that undergo routine evaluations during an investigation for bone loss may have increased levels of PTH, even without hypercalcemia [21].

The term normocalcemic primary hyperparathyroidism (NPHPT) was first used by Wills in 1960, who described a group of patients having characteristics different to those diagnosed with classic PHPT [22].

NPHPT is characterized by levels of serum calcium that remain normal while PTH levels are high [23–25]. Since there is a greater availability and utilization of assays for the evaluation of this hormone, this condition has been frequently diagnosed. However, examining for other causes of secondary hyperparathyroidism, especially 25-hydroxyvitamin D deficiency, is necessary to confirm the diagnosis [8, 25].

Little is known about the epidemiology of NPHPT. In Sweden, Lundgren et al. studied 5,202 postmenopausal women aged 55–75 years.

In the 109 subjects studied, the researchers investigated two indices, observing whether the patients presented hypercalcemia associated with increased levels of PTH and higher levels of either hypercalcemia or PTH. Seventeen (16 %) out of the 109 subjects studied had normal levels of serum calcium (<9.9 mg/dL) and increased PTH. This group of 17 subjects included people that had vitamin D deficiency as well as patients with NPHPT [26].

It remains debatable whether NPHPT incipiently represents classic PHPT or a different spectrum of this pathology [24]. Evidence suggests that patients without secondary causes of hyperparathyroidism may have early-stage PHPT since, if the disease is diagnosed early, it can progress with isolated increased serum PTH, which may or may not be followed by an increase in serum calcium. For these patients, serum calcium should be periodically evaluated during the development of the disease [25, 27].

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## Skeletal Manifestations

The skeletal complications of PHPT are well known. Among the classic symptoms, these complications are considered the most familiar consequences of PHPT. The clinical presentation may include focal or widespread bone pain, localized bone edema (“brown tumors”), and fragility fractures [21].

Intense bone demineralization is seen in X-rays of patients with this severe disease. Pathological fractures are frequently seen, especially in the long bones of the lower extremity, and also loss of the lamina dura of the teeth and brain lesions in the salt-and-pepper pattern which refers to the speckled appearance of the tissue. Subperiosteal bone erosions in the distal phalanges and on the edges of the medial phalanges are usually seen as numerous lytic lesions with irregular sclerotic margins, which are more common in the pelvis, long bones, and shoulders. The cortical bone of the long bones is extremely thin and in some patients is almost absent [16].

Bone densitometry is a useful tool for investigating the classic effects of PTH, such as reduction in bone mineral density (BMD) in the distal

radius, the site of the cortical bone. The catabolic ability of PTH on the cortical bone is the opposite of its anabolic effect on cancellous bone. In the lumbar spine, the site of cancellous bone, BMD seems to be normal. The hip contains a more uniform mix of cortical and cancellous bone elements and the BMD is classified as being of an intermediate density between the distal radius and the lumbar spine. Although this classic densitometric profile is usually seen as a distinct pattern characterized by vertebral osteopenia, it can also be seen at the moment of diagnosis. In the more severe types of PHPT, there is an overall decrease in bone density [28].

The prevalence of PHPT and its impact on BMD were evaluated in 3,014 men aged 69–81 years in a Swedish cohort, *MrOs*. Subjects with a low glomerular filtration rate ( $<21$  mL/min/1.73 m<sup>2</sup>) and vitamin D deficiency ( $<50$  nmol/l) were excluded from the study. BMD was compared between patients with and without PHPT. The prevalence of PHPT was estimated to be 0.73 %. BMD in the total hip and femur neck was lower among the PHPT group than in the control group. Subjects with high levels of intact PTH were compared with the other subjects from the cohort. For that subgroup, BMD was lower for the total hip and lumbar spine ( $p < 0.05$ ) [29].

A controlled clinical trial compared two groups: (1) carriers of mild PHPT that were submitted to parathyroidectomy ( $n=25$ ) and (2) patients that had an intact parathyroid ( $n=28$ ). After 24 months, there was a significant increase in the BMD in the femur neck and total hip, but not in the lumbar spine or forearm of patients submitted to parathyroidectomy when compared with those that did not undergo a parathyroidectomy. There was also a decrease in the biochemical markers of bone remodeling after parathyroidectomy [30]. Another study with 11 patients, including a 5-year follow-up after parathyroidectomy, showed a significant BMD increase in the lumbar spine. However, neither the hip nor the distal radius showed any BMD increase when compared to baseline values. They also observed a reduction in the markers for bone remodeling [31].

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## Extraskeletal Manifestations

### Neuropsychiatric Symptoms

In addition to skeletal manifestations, PHPT may be associated with alterations in other organ systems within the body. Neuropsychiatric symptoms can occur in about 23 % of patients with PHPT, such as fatigue, difficulty concentrating, irritability, and mood and sleep disorders [32]. Since few studies have evaluated the prevalence of these manifestations, they remain uncertain [33]. A case–control study compared 39 postmenopausal patients with mild PHPT and 89 women without PHPT. This study revealed a higher prevalence of depression and anxiety and a higher performance on tests for verbal and nonverbal memory in the PHPT carriers. Also observed was the fact that depressive symptoms, nonverbal abstraction, and aspects of the verbal memory were significantly improved after parathyroidectomy [34]. Peripheral neurological alterations, especially sensory–motor polyneuropathy and PHPT, have been suggested by some authors [35, 36]. Recent data report clinical improvement after surgical treatment, which is recommended in patients that have neurological symptoms related to PHPT and do not present any contraindication for surgery [37].

### Cardiovascular Symptoms

The literature shows a relationship between PHPT and abnormalities such as arterial hypertension, left ventricular hypertrophy, abnormal heart function, coronary artery disease, vascular abnormalities, conduction disorders, and valvular and myocardial calcification [38]. The mechanism for this aforementioned relationship remains uncertain, but it has been shown that morbidity and the risk of cardiovascular death are greater in PHPT carriers. This is mainly observed in patients with the mild to severe form of the disease [39]. On the other hand, parathyroidectomy decreases cardiovascular risk, as shown in a num-

ber of population studies, even with mild forms of the disease. Surgery is therefore indicated in all patients with PHPT and other factors of cardiovascular risk [40, 41].

### Other Extraskeletal Manifestations

Nephrocalcinosis and nephrolithiasis are also clinical manifestations of asymptomatic and NPHPT. From the experience of our group, a recent study demonstrated an 18.2 % rate of nephrolithiasis in NPHPT patients, as well as in the hypercalcemic modality (18.9 %), may have show a non-indolent presentation [42].

### Localization of Parathyroid Lesions

Imaging examinations are not indicated for the diagnosis of PHPT. The location of the affected parathyroid is an indication for surgery and can permit the use of less invasive techniques, which is associated with a lower morbidity rate [43]. Ultrasonography and Sestamibi scintigraphy are the most common techniques used for PHPT diagnosis (Figs. 22.1 and 22.2). Cervical ultraso-

nography is a low-cost examination, as well as noninvasive. When performed by an experienced examiner, it presents a sensitivity and specificity of 88 and 94 %, respectively [44]. In cases of ectopic glands or an intrathyroid adenoma, identification and differentiation of thyroid nodules can be difficult. Thus, ultrasonography coupled with  $^{99m}\text{Tc}$ -labeled Sestamibi scintigraphy increases the chance of identification to almost 100 % of the lesions [45]. These two methods are complementary, since ultrasonography provides anatomic information while the scintigraphy provides functionality data.

Scintigraphy is able to identify the topic and ectopic parathyroid tissues. A study with 64 PHPT patients presented positive scintigraphy in 64 % of the patients that had asymptomatic PHPT and 83 % of the group that carried nephrolithiasis without bone involvement. That same study showed that 100 % of the subjects with the severe disease presented positive scintigraphy as well, but in this case it was characterized by osteitis fibrosa cystica. These results were found when the imaging was evaluated early, which occurred in 70 % of the cases analyzed [45] (Fig. 22.3). A small number of patients may have negative imaging, which suggests multiglandular disease. In these cases, the use of the most advanced imaging techniques may be necessary to increase the chances of localizing the affected parathyroid and ectopic tumors, and also assist in the decision to proceed with surgery. Four-dimensional computed tomography was able to localize the adenoma with 82 and 92 % sensitivity and specificity, respectively, in 34 PHPT patients [46]. A retrospective trial found almost 100 % specificity in the diagnosis of multiglandular disease in 35 patients evaluated; however the sensibility was much lower (42.9 %). As regards the localization of only one lesion, they were able to identify 32 cases with a sensibility of 91 % [47]. The preoperative localization of an adenoma allows the use of minimally invasive parathyroidectomy (MIP) with lower morbidity and can be done in an outpatient facility [47].

One of the main disadvantages of imaging examinations is the high incidence of false-positive results due to the size and localization of



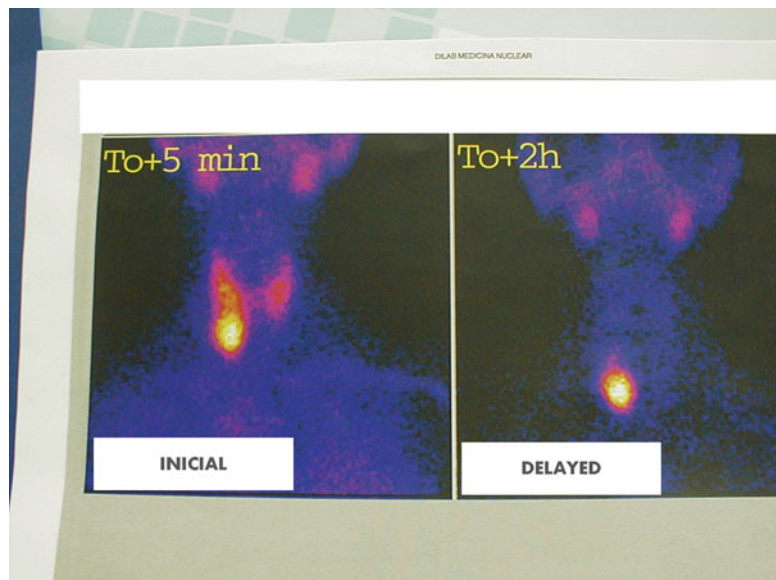
**Fig. 22.1** Tc-99-Sestamibi scintigraphy showing a right inferior parathyroid lesion



**Fig. 22.2** Cervical ultrasound from the same patient in Fig. 22.1



**Fig. 22.3**  $^{99m}\text{Tc}$ -Sestamibi scintigraphy showing a large parathyroid adenoma



the parathyroid affected. As a result, fine needle aspiration of the nodule that was identified by imaging for measurement of PTH in the aspirated material has become an auxiliary method for diagnosing lesions, as shown by a study performed by our group. A group of 15 women without PHPT, who had nodules identified by

ultrasonography, showed very high PTH levels, presenting a mean of  $4.919 \pm 5.124$  pg/mL whilst the control group had a mean of  $10.65 \pm 3.49$  pg/mL. This technique showed a greater sensitivity in locating the affected gland than the use of imaging alone [48]. The main methods for locating parathyroid lesions are shown in Table 22.3.

**Table 22.3** Localization procedures for the identification of parathyroid adenoma

Methods	Sensitivity (%)	Specificity (%)
Cervical ultrasonography (US)/Doppler US	88/97	94/100
Computed tomography fourth dimension	82	92 a 100 <sup>a</sup>
Technetium-99 m Sestamibi scintigraphy	90 <sup>b</sup>	100
PTH measurement in aspiration fluid (FNA <sup>c</sup> )	100	100

Adapted from refs. [43–46]

<sup>a</sup>The specificity for multiglandular disease is close to 100 %

<sup>b</sup>The sensitivity increases in more serious cases being close to 100 % in patients with osteitis fibrosa cystica. The accuracy is lower in multiglandular disease

<sup>c</sup>FNA fine needle aspiration

## Indications for Parathyroidectomy in PHPT

Parathyroidectomy is the treatment of choice for patients with PHPT, but indicating surgery for subjects in whom a parathyroid lesion was not found may need some criteria. The aim of surgery is to provide treatment by removal of the affected parathyroid. This occurs in 95–98 % of the patients operated on by an experienced surgeon, with the number of complications being low. According to the Third International Workshop, surgery is indicated for asymptomatic patients if there is a greater benefit than with drug treatment [49]. Table 22.4 lists the conditions in which surgery is particularly indicated:

- Symtomatic patients
- Patients with a history of fragility fractures or osteoporosis shown by a bone densitometry (T-score below  $-2.5$  in one of the skeletal sites: lumbar spine, femur neck, or distal radius)
- Patients under 50 years old
- Patients with creatinine clearance lower than 60 mL/min/1.73 m<sup>2</sup>
- Patients with 1 mg/dL blood calcium above the reference value

**Table 22.4** Surgical indications for asymptomatic primary hyperparathyroidism

Nephrolithiasis
Osteitis fibrosa cystica
Serum calcium >1 mg/dL above ULN <sup>a</sup>
Creatinine clearance <60 mL/min/1.73 m <sup>2</sup>
T-score < $-2.5$ at the lumbar spine, hip, and/or distal radius
Age <50 years
Patients whose medical monitoring is not possible

<sup>a</sup>ULN upper limit of normality  
Adapted from ref. [47]

With regard to the minimal significant alterations in the bone loss rate during the natural disease progression, asymptomatic PHPT patients who do not meet the criteria for surgery or patients that have some contraindication should have their BMD monitored by biannual bone densitometry (dual-energy X-ray absorptiometry—DXA) [49]. The patients with a vitamin D deficiency (serum levels of 25-OHD below 20 ng/mL) should receive adequate replacement, in accordance with the recommendations for patients without PHPT [39].

Randomized studies [34, 50, 51] have demonstrated the benefits on the quality of life and on BMD of asymptomatic patients submitted to surgery. Even though these studies were randomized, they had a short follow-up period. Finally, another important point about MIP is that this procedure yields excellent results, produces few complications, and decreases the cost of a surgical procedure [52].

## Surgical Techniques

Bilateral cervical exploration is the traditional surgical technique, and consists of the evaluation and removal of the affected parathyroid glands. However, the morbidity, surgical duration, and risks of complications are greater. The early localization of the lesion therefore allows the use of MIP as mentioned above [52].

A prospective, randomized, and blinded study compared MIP with conventional parathyroidectomy in 48 patients with PHPT. In the group sub-

mitted to MIP, there was a lower pain intensity in the postoperative period ( $p < 0.001$ ), less use of analgesics ( $p < 0.001$ ), a lower rate of anesthesia procedures ( $p < 0.001$ ), a smaller scar ( $p < 0.001$ ), and greater aesthetic satisfaction postoperatively at 2 days, 1 month ( $p < 0.01$ ), and 6 months ( $p < 0.05$ ); however 1 year after surgery aesthetic satisfaction was no longer significantly different in the two groups ( $p = 0.38$ ). On the other hand, there was a higher cost with MIP and no significant difference in the quality of life in either group 6 months after the surgical procedure [53].

### Intraoperative PTH Monitoring

This procedure is used during MIP for the treatment of PHPT. As regards the time frame for intraoperative PTH monitoring, this is performed after the anesthesia, before the skin incision, and ten minutes after removal of the enlarged gland [54]. One can observe a fall of less than 50 % in the PTH levels, when compared with the baseline values. This fall of less than 50 % shows the risk of persistent disease. Several studies have analyzed how useful the intraoperative PTH evaluation can be, and they suggest that this measurement should be indicated in cases (1) that present only an imaging study during preoperative care of positive MIP; (2) when the imaging studies for preoperative localization are discordant; and (3) of reoperation [54–57].

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### Medical Therapy

Drug therapy is indicated for patients contraindicated for surgical treatment, those with therapy failure, and patients that either do not want the surgical procedure or did not meet the current criteria. Among the options to replace a surgical procedure is cinacalcet, which acts as a calcimimetic and is able to decrease the PTH release. Other options are an antiresorptive agent which inhibits bone remodeling, for example a bisphosphonate, hormone therapy, and selective modulators of estrogen receptors [39].

### Calcimimetic Agents

Calcimimetic agents are drugs that can increase the sensitivity of the calcium-sensing receptor to extracellular calcium, which results in a reduction of PTH. The first calcimimetic developed was a derived phenylalkylamine (R-568); however it had low availability and a high variability of response. As a result, cinacalcet hydrochloride, with higher availability and a lower pharmacologic variability, was developed [58]. Studies show that cinacalcet decreases PTH levels by up to 50 %, and is thus able to regulate serum calcium in approximately 80 % of treated patients [58]. The recommended starting dose for PHPT is 30 mg once daily which may be adjusted up to 300 mg/day [58].

A multicenter, randomized, double-blind, placebo-controlled study evaluated 78 patients with PHPT to ascertain the long-term ability of cinacalcet to reduce serum calcium and PTH. The patients received a dose starting at 30 mg, twice a day; if there was a persistent hypercalcemia, the dose was increased to 40–50 mg during a 12-week period. The final dose was maintained for 12 weeks and patients were followed for another 28 weeks. Two doses per day of cinacalcet decreased serum calcium by 0.5 mg/dL or more and normalized (calcium  $< 10.3$  mg/dL) in 73 % patients treated during a maintenance phase, and also decreased levels of PTH by 7.6 % over the same period [59]. Serum calcium levels remained normal and PTH remained lowered for up to 52 weeks.

With regard to BMD measured by dual-energy X-ray densitometry (DEXA), no significant changes were found during the 52-week period or the following 5 years [60, 61]. Cinacalcet significantly increased some of the markers of bone remodeling (bone alkaline phosphatase and NTx), and the rate of NTx/urinary creatinine for 52 weeks, when compared with the placebo group, however remained within the normal range [60].

The use of calcimimetics is indicated for those patients that have hypercalcemia related to renal insufficiency of the tertiary hyperparathyroidism, for those who are carriers of parathyroid carcinoma, or when there is a contraindication for surgery [58].

## Hormone Replacement Therapy

The use of estrogens is a therapeutic option for postmenopausal women because it increases BMD in the femoral neck and lumbar spine. This protective effect from fractures was demonstrated in the WHI trial with the use of conjugated estrogens at a dose of 0.625 mg together with a daily 5 mg dose of medroxyprogesterone for 2 years [62]. Nevertheless, their long-term use is not indicated, since they also increase the risk of cardiovascular and breast cancer. Thus one should analyze the risks and benefits before suggesting this therapy [62].

Furthermore, another randomized, double-blind, placebo-controlled study with 42 menopausal women with PHPT over 2 years evaluated the effects of conjugated estrogens at a dose of 0.625 mg, together with a daily 5 mg dose of medroxyprogesterone on BMD, biochemical parameters of bone remodeling, and calcium metabolism. In this study, there was a reduction in total serum calcium, but no changes in the ionized calcium and intact PTH. Regarding the markers of bone remodeling, there was a 22 % decrease in alkaline phosphatase and a 38 % decrease in urinary hydroxyproline excretion was also observed. In addition, 60 and 33 % reductions were found in N-telopeptide excretion and urinary calcium excretion, respectively [63]. This therapy showed positive effects on the total BMD of the body, lumbar spine, femur, and forearm over the 2 years. These positive effects remained for at least the 4 years of follow-up [64].

Estrogen therapy may thus be the treatment of choice for women that have bone loss and PHPT in the postmenopausal period. This therapy should be indicated if there is no contraindication for its use.

## Selective Modulators of Estrogen Receptors (SERMs)

Nowadays, there is little evidence in the literature concerning the selective modulators of estrogen receptors (SERMs). A randomized, double-blind,

placebo-controlled investigation, with 18 patients demonstrated the efficacy of 60 mg/day raloxifene in reducing both serum calcium levels and markers of bone remodeling (serum NTx and osteocalcin) over an 8-week period. After 4 weeks of treatment with raloxifene, there were no alterations in the calcium and PTH levels. Moreover, during the same period, the markers of bone remodeling returned to baseline values [65].

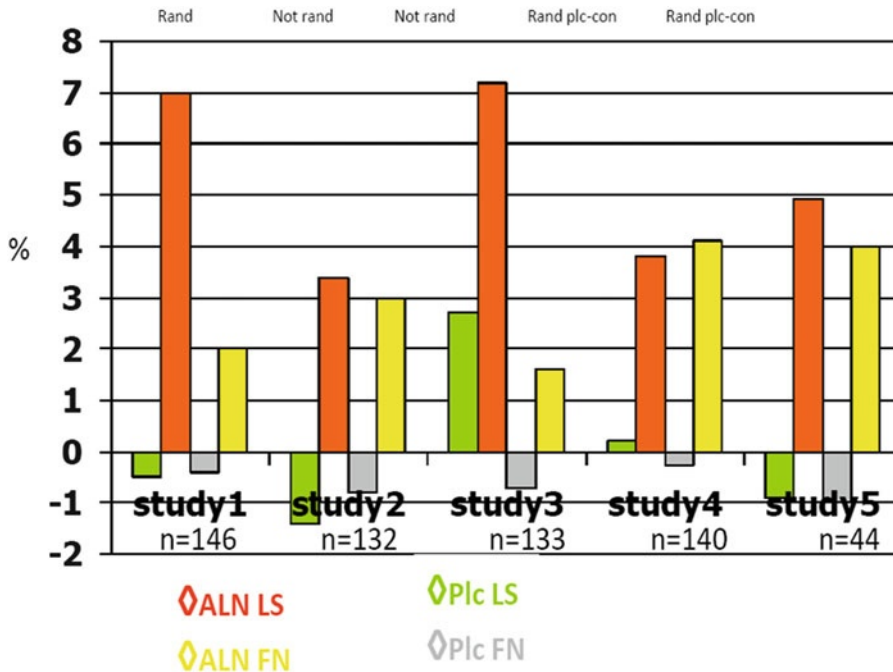
## Bisphosphonates

The bisphosphonates, administered to patients with PHPT, have proven their efficacy in the improvement of bone mass as compared to a placebo, which was measured by DEXA. The use of oral alendronate has been evaluated in five studies involving 119 postmenopausal women and 24 men treated for 2 years (Fig. 22.4). The results showed a significant increase in BMD at the lumbar spine and femoral neck, but no substantial change in density of the distal radius. There was also a decrease in the levels of calcium adjusted for albumin and a decrease in PTH and markers of bone turnover [66–70].

Another example [70] is a double-blind, controlled trial with 44 patients who did not undergo parathyroidectomy and used alendronate (10 mg/day) for 2 years. In this case, the study showed a gain in bone mass in the lumbar spine and femoral neck, but there were no changes in calcium or PTH levels. Markers of bone turnover had reduced levels without modifying the risk of fractures.

Jansson and Cols [71] evaluated 21 patients with PHPT who were given 30–40 mg of pamidronate before surgery. A temporary reduction in the levels of serum calcium was observed with the nadir after 6–10 days of infusion, and a return to high levels after this period.

In conclusion, alendronate may represent a therapeutic option and the possibility of bone protection, albeit with no prospect of achieving long-term normocalcemia, and may be associated with increased levels of serum PTH.



**Fig. 22.4** Clinical trials on alendronate therapy for PHPT

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Malachi J. McKenna and Barbara Murray

## Introduction

Vitamin D, which is present in two forms called cholecalciferol ( $D_3$ ) and ergocalciferol ( $D_2$ ), is an essential micronutrient and in the bioactive form plays a key role in maintaining bone health [1]. Vitamin  $D_3$  is predominantly derived from skin production by the direct action of ultraviolet light on skin. Alternative sources of  $D_3$  and  $D_2$  are oral intake from natural foodstuffs, fortified foodstuffs and supplements. Although the principal source is sunlight, oral intake has primacy over sunlight exposure in both the prevention and correction of privational vitamin D deficiency [2]. Sunlight exposure can be a cause of skin cancer and for this reason cannot be advocated as a means to prevent vitamin D deficiency. In determining the oral intake that is required to meet the needs both to prevent and to correct vitamin D deficiency one must take into account inadvertent and intentional exposure to sunlight. In other words, the recommended daily allowance for vitamin D as an oral nutrient need only be specified for those who are

sun-deprived; those who are not sun-deprived have lower oral intake requirements [3].

Vitamin D is activated by two metabolic steps: first, hydroxylation to 25OHD in the liver that is substrate dependent on sources of parent vitamin D; then, further hydroxylation by  $1\alpha$ -hydroxylase in the kidney to the hormonal or active form,  $1\alpha,25$ -dihydroxyvitamin D ( $1,25(OH)_2D$ ) that is tightly regulated by PTH and FGF23 [4]. The hormonal form then circulates to remote sites of action and binds to the vitamin D receptor (VDR), principally at the intestine promoting absorption of calcium and phosphorus. The mineral-product of calcium and phosphorus is essential for the mineralization of newly formed bone matrix at all stages of life. The final activation step occurs also in extrarenal tissues followed by local binding to VDR, which is termed the paracrine/intracrine effect. This intracrine effect is not regulated by calciotropic hormones but by tissue-specific cytokines and is substrate dependent [5]. This is a more complicated aspect of vitamin D action, which is the subject of much basic and clinical research over the past two decades.

Severe vitamin D deficiency leads to rickets in the growing skeleton and osteomalacia in the adult skeleton. In adults, it also predisposes to low bone mass and contributes to bone fragility fractures in the elderly. Deficiencies in the intracrine action may account for associations between vitamin D deficiency and infections, autoimmune disease, cardiovascular disease, diabetes mellitus, falls and cancer, but according to a recent report from the Institute of Medicine

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(IOM), which was commissioned for the governments of Canada and the USA, the evidence for causality is inconsistent and inconclusive [3, 6]. On the contrary, the IOM report concluded that there was a well-established causal link between vitamin D intake and skeletal health [3].

**Key Points**

**Definition of Vitamin D Deficiency**

It is probably best for clinicians to divide vitamin D deficiency into two groups: those who are sun-deprived; and those who have intestinal, liver or kidney disorders. The correct term for the former is “privational” not “nutritional” vitamin D deficiency. Privational encompasses the role of both sources of vitamin D: sunlight exposure and oral intake. It is incorrect to apply the terms “deficiency” or “insufficiency” based on 25OHD levels. Although measuring 25OHD level has a prime role in assessing vitamin D status (see

later); it is not a clinical outcome; it is merely a measure of risk of disease [3, 6, 7].

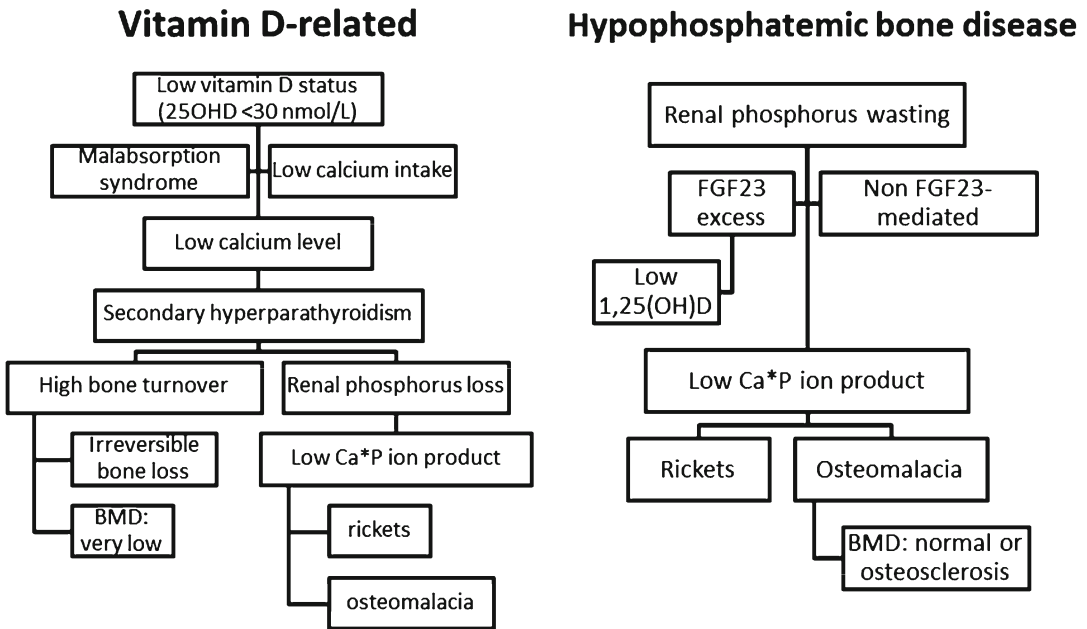
There has been a double paradigm shift since the 1990s: first, the term hypovitaminosis D was replaced by the terms “deficiency” and “insufficiency” implying the presence of a disease state; and, second, the 25OHD thresholds have steadily increased from 25 nmol/L (10 ng/ml) to 75 nmol/L (30 ng/ml). The recent IOM report states that 25OHD is an estimate of risk of clinical outcomes, and that risk of skeletal disease reaches a plateau at 30–40 nmol/L (12–16 ng/ml) (see below and Table 23.1) [3, 6–8].

Privational vitamin D deficiency is best defined as a clinical, biochemical, radiologic, densitometric or histomorphometric abnormality that is corrected and prevented by low dose vitamin D supplementation [9]. The natural history of vitamin D-related bone disease at the bone level is a phase of secondary hyperparathyroidism (SHPT) with accelerated irreversible bone loss culminating in a mineralization defect (rickets or osteomalacia). Once the entire surface of bone is

**Table 23.1** Implications for clinical practice of the 2011 IOM report on dietary reference intakes

Sun-deprivation	The vitamin D specifications apply to individuals with minimal or no sunlight exposure. This encompasses housebound individuals especially the frail elderly, those who practice concealment for cultural or religious reasons, those with darker skin, those that apply high factor sunscreen, and those residing in high-latitude countries during the months when there is absent skin generation of vitamin D. These otherwise healthy individuals are at risk of reduced vitamin D synthesis.
Dietary reference intakes (DRIs)	Estimated average requirement (EAR): meets the needs of 50 % of the population. The EAR is an appropriate estimate when considering intake for groups or persons. The recommended daily allowance (RDA) meets the needs of over 97.5 %. The RDA is likely an overestimate of need for any particular individual; but since the true requirement of an individual may not be known, the clinician may aim for this higher intake level.
Vitamin D status as judged by serum or plasma 25OHD level	25OHD is considered a “biomarker of exposure” (namely, the best measure of vitamin D supply) but it is not a “biomarker of effect” (namely, it is not a clinical outcome). The plateau of skeletal benefit is reached at 30–40 nmol/L (12–16 ng/ml). The EAR corresponds to a 25OHD level of 40 nmol/L (16 ng/ml). The RDA corresponds to a 25OHD level of 50 nmol/L (20 ng/ml).
Current vitamin D status in USA	In the USA, the median oral intake of vitamin D is less than 400 IU/d but the mean 25OHD levels are above 50 nmol/L. The 25OHD level is higher than expected for vitamin D intake; this suggests, not surprisingly, that supply from sun-light exposure either inadvertent or intentional contributes substantially to vitamin D status. This reinforces the point that the EAR and RDA apply to sun-deprived individuals.
Safe vitamin D intake level and safe 25OHD level	The tolerable upper intake level is defined by the IOM report as the upper level of vitamin D intake beyond which harm could be expected to increase for the general population. The IOM specified that this threshold is 4,000 IU daily, and also specified that this not to be considered as a target intake. Furthermore, IOM specified that a 25OHD level of 125 nmol/L (40 ng/ml) corresponds with this upper intake level.
Calcium intake	The clinician must also consider the EARs and RDAs for calcium intake.

## Pathways to Rickets and Osteomalacia



**Fig. 23.1** BMD=bone mineral density; FGF23=fibroblast growth factor 23; Ca=calcium; P=phosphorus; 25OHD=25-hydroxyvitamin D; 1,25(OH)<sub>2</sub>D=1 $\alpha$ ,25-dihydroxyvitamin D

covered in unmineralized bone matrix (osteoid), irreversible bone loss ceases [10]. On the contrary for hypophosphataemic bone disease, the natural history is one of progressive mineralization defect [11]. This understanding is important in addressing differential diagnosis (Fig. 23.1).

### Measuring 25OHD

Serum or plasma 25OHD is the best measure of vitamin D status because its synthesis is substrate dependent and it has a long half-life of about 2 weeks [12]. There are two types of assay for detecting total 25OHD, 25OHD<sub>3</sub> and 25OHD<sub>2</sub>: (1) immunoassays and automated immunoassays for total 25OHD; and (2) high pressure liquid chromatography (HPLC) liquid chromatography tandem mass spectrometry (LC-MS/MS) and isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) for 25OHD<sub>3</sub> and 25OHD<sub>2</sub>.

One of the major factors contributing to analytical uncertainty in 25OHD testing is the lack of standardization of 25OHD methods [13–16]. Intermethod variability should improve following the introduction in 2009 of Standard Reference Materials (SRM 972) and solvent-based primary calibrators (SRM 2972) by the American National Institute of Standards and Technology (NIST), and also following the acceptance by the Joint Committee for Traceability in Laboratory Medicine (JCTLM) of the NIST and University of Ghent assays (ID-LC-MS/MS and ID/LC/MS) as reference measurement procedures (RMPs) [17]. However, 3 of the 4 SRM 972 reference materials are either spiked with exogenous metabolites (Level 3 with 25-hydroxyvitamin D<sub>2</sub>, and Level 4 with 3-epi-25-hydroxyvitamin D<sub>3</sub>) or diluted in horse serum (Level 2) which makes these levels unsuitable for many immunoassays. Only the SRM 972 Level 1 pool should be used for standardization purposes in immunoassays [18]. A new generation of human serum-based

SRMs are due to be released that should further improve assay standardization.

Many of the automated immunoassays, which do not have preliminary solvent extraction or protein precipitation to free 25OHD from vitamin-D-binding proteins (DBPs), are subject to DBP matrix interferences [16]. Also for immunoassay techniques, a measure of total metabolite concentration and equivalent detection of both 25OHD<sub>2</sub> and 25OHD<sub>3</sub> is challenging, because binding proteins show a higher affinity for 25OHD<sub>3</sub> than 25OHD<sub>2</sub> [19]. All immunoassays have a high cross-reactivity with the metabolite 24,25-dihydroxyvitamin D, which can be present in serum at concentrations of up to 12 nmol/L [20]. LC-MS/MS methods have been shown to suffer from two interferences: the C-3 epimer of 25OH D<sub>3</sub>, and isobaric substance 7- $\alpha$ -hydroxy-4-cholesten-3-one [21, 22]. The NIST standard containing 3-epi-25OHD<sub>3</sub> (SRM 972 Level 4) allows laboratories to check whether or not their method suffers from interference from this metabolite. The isobaric substance has been separated by a novel LC-MS/MS method [21].

It is challenging for clinicians to assess multiple 25OHD results for a given patient if performed at different laboratories using different methods of measurement [23]. It is important for clinicians to be provided by their 25OHD service providers with their assay limitations with regard to traceability, specificity, imprecision and limit of detection. Their participation in a proficiency testing scheme such as the International Vitamin D External Quality Assessment Scheme (DEQAS) is essential [24]. Clinicians should be alerted to any change of methodology as this could have a significant impact on results, patient classification, and treatment recommendations. Finally, clinicians need to ignore reference ranges for 25OHD from commercial laboratories that quote inordinately high levels for vitamin D status [7].

## IOM and Defining Vitamin D Status

Vitamin D status should be considered in the light of the recent IOM report, which revised the dietary reference intakes (DRIs) for the USA and Canada (Table 23.1). The 2011 IOM report is

now the standard on vitamin D requirement and on vitamin D status because it examined the totality of evidence with respect to harms and benefits for both calcium and vitamin D for the entire population [8]. Using a risk assessment framework they specified the estimated average requirement (EAR) that meets the need of approximately 50 % of the population, and the recommended daily allowance (RDA) that meets the need of 97.5 % of the population (Table 23.2). They specified that a 25OHD level of 40 nmol/L (16 ng/ml) corresponded to the EAR and that a level of 50 nmol/L (20 ng/ml) corresponded to the RDA [3, 7, 25].

The implications of the IOM report for clinical practice are summarized in Table 23.1. The IOM report avoided using the terms “vitamin D deficiency” and “vitamin D insufficiency” when defining vitamin D status. Appropriate terms included “hypovitaminosis D” or “low vitamin D status” for a result below 30 nmol/L (12 ng/ml); and “vitamin D adequacy” or “vitamin D sufficiency” for levels 30–50 nmol/L (12–20 ng/ml). Just as there is a range of requirement for vitamin D intake, so is there a corresponding range of adequacy or sufficiency for 25OHD [7]. The RDA and the corresponding 25OHD of 50 nmol/L (20 ng/ml) is likely an overestimate of the need for any particular individual; but since the true requirement of an individual may not be known, the clinician may aim for this higher 25OHD level in defining adequacy or sufficiency [7, 8]. The IOM report expressed concern about levels above 125 nmol/L (50 ng/ml) based on emerging evidence about risks that could not be defined in the usual terms of vitamin D toxicity.

## Secondary Indices of Vitamin D Deficiency (Fig. 23.2)

If 25OHD is below 30 nmol/L (12 ng/ml), then the practitioner should encourage an augmented oral intake (see treatment section below), but does not necessarily need to embark on additional investigations. Much lower levels may be associated with clinical features including proximal myopathy and diffuse bone pain. Secondary biochemical indices include hypocalcaemia and hypophosphataemia.

**Table 23.2** Dietary reference intakes for calcium and vitamin D as specified by 2011 IOM report

Life stage group	Calcium mg/d			Vitamin D IU/d		
	EAR	RDA	UL	EAR	RDA	UL
Infants 0–6 months	*	*	1,000	**	**	1,000
Infants 0–12 months	*	*	1,500	**	**	1,500
1–3 years old	500	700	2,500	400	600	2,500
4–8 years old	800	1,000	2,500	400	600	3,000
9–13 years old	1,100	1,300	3,000	400	600	4,000
14–18 years old	1,100	1,300	3,000	400	600	4,000
19–30 years old	800	1,000	2,500	400	600	4,000
31–50 years old	800	1,000	2,500	400	600	4,000
51–70 years old	800	1,000	2,000	400	600	4,000
51–70-year-old females	1,000	1,200	2,000	400	600	4,000
71+ years old	1,000	1,200	2,000	400	600	4,000
14–18 years old, pregnant/lactating	1,100	1,300	3,000	400	600	4,000
19–50 years old, pregnant/lactating	800	1,000	2,500	400	600	4,000

\*For infants, adequate intake is 200 mg/d for 0–6 months of age and 260 mg/d for 6–12 months of age. The adequate intake is used when an EAR/RDA cannot be developed; it is the average intake level based on observed or experimental intakes; and it is likely greater than the needs of most infants

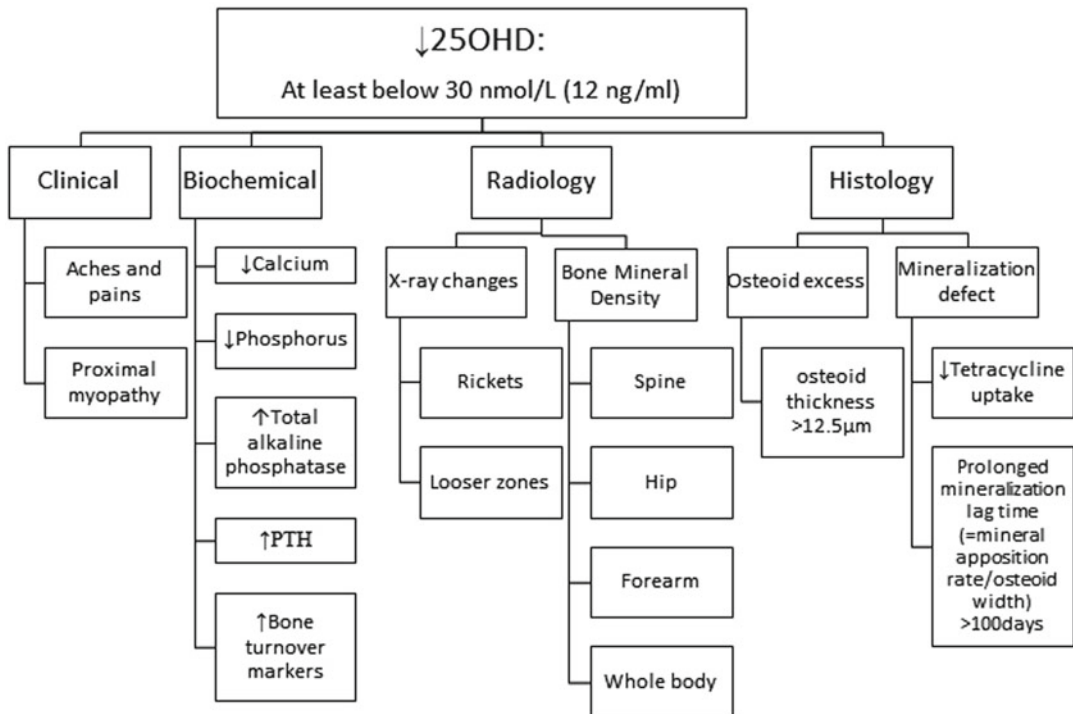
\*\*For infants, adequate intake is 400 IU/d for 0–12 months of age

EAR=estimated average requirement that meets the needs of 50 % of the population

RDA=recommended daily allowance that meets the needs of 97.5 % of the population

UL=upper intake tolerable level

## Indices of Vitamin Deficiency



**Fig. 23.2** 25OHD=25-hydroxyvitamin D; PTH=parathyroid hormone

Although not calculated in clinical practice, the calcium–phosphorus ion product is a measure of the degree of deficiency that links directly with the consequence of a mineralization defect in bone. Another simple measure that is routinely available is serum total alkaline phosphatase; in the absence of liver disease it is a direct marker of bone disease.

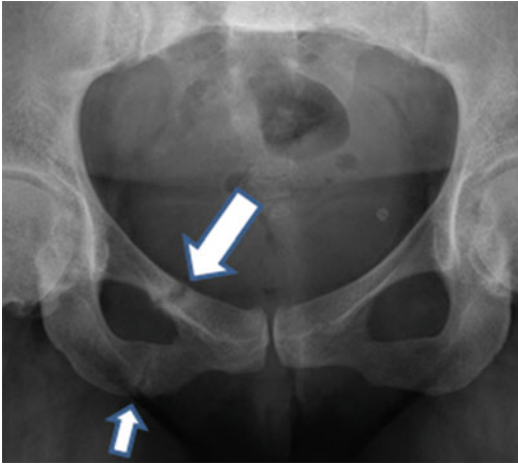
Serum PTH should be measured as part of the assessment. Secondary hyperparathyroidism (SHPT) occurs in response to hypocalcaemia. This results in an increase in bone turnover as part of the effort to restore calcium homeostasis. In addition,  $1\alpha$ -hydroxylase activity is augmented such that  $1,25(\text{OH})_2\text{D}$  levels may be elevated in vitamin D deficiency; this metabolite is not a measure of vitamin D status. Renal tubular effects of SHPT such as renal phosphorus wasting and renal bicarbonate wasting may hasten the onset of the mineralization defect in bone. Other factors influence PTH status such as calcium intake, renal function, age, ethnicity, body composition and geographic location [8]. There is no single threshold level of  $25\text{OHD}$  that prevents secondary hyperparathyroidism [3, 8, 26].

An array of bone turnover markers is available for assessing bone status [27]. An increase in bone formation markers may reflect either an increase in bone remodelling activity due to SHPT or a defect in mineralization, or both. They are serum-based and should be collected in the fasting state (bone specific alkaline phosphatase, procollagen type I aminopropeptide and osteocalcin), whereas increased resorption markers only reflect SHPT. They include: (1) fasting serum-based tests such as beta-C-terminal cross-linking telopeptide of type I collagen ( $\beta$ -CTX), N-terminal cross-linking telopeptide of type I collagen (S-NTX), and tartrate-resistant acid phosphatase 5b (TRAP5b); and (2) either a timed-fasting urine or fasting second void urine or a 24-h urine collection for urinary NTX (U-NTX). Clinicians should obtain protocols from their laboratory service provider for instructions on specimen type required. It should be noted that reduced renal function may lead to reduced urinary excretion of  $\beta$ -CTX and a consequent increase in the apparent serum  $\beta$ -CTX con-

centration. Urinary markers of bone metabolism should be omitted in patients with renal insufficiency and a creatinine clearance of  $<20$  ml/min [28]. In vitamin D deficiency both formation and resorption markers are increased, but in hypophosphataemic bone disease only formation markers are increased.

Specific radiographic changes occur late in the course of vitamin D deficiency. Rickets is a disease of the growing skeleton with radiographic changes being most pronounced at the growth plates in those bones that are growing fastest such as around the knee, the wrist especially the distal end of the ulna, the middle ribs, the proximal femur and the distal tibia. Initially the growth plate widens as a consequence of defective mineralization between epiphysis and metaphysis [29]. Then the metaphyseal surfaces become cupped and irregular. This is accompanied by splaying of the metaphyses and widening of the growth plates that accounts for the classical clinical signs of swelling at the wrists, knees and anterior ends of the ribs (rickety rosary). Bone deformities occur principally in lower extremities in weight-bearing bones resulting in knock knees, bow-legs, wind-swept legs [29, 30].

Insufficiency-type stress fractures in the setting of osteomalacia are referred to by the eponymous term, Looser zones [29]. They are often incorrectly called “pseudofractures”. It has been recommended for many years that this term is of no further value [31]. Looser zones are stress fractures. They are usually multiple in origin and are often symmetric in occurrence. They occur at typical sites in both weight-bearing bones (such as pubic rami, medial aspects of the femur and tibia, and metatarsal bones) and non-weight bearing bones (such as ribs, and medial border of the scapula). Appearances are characteristic in that the fracture appears as a broad rather than a narrow band, margins are parallel, marginal sclerosis is minimal, callus is usually present, but healing is delayed (Fig. 23.3). Typically, they only occur late as a manifestation of osteomalacia. Traditionally, they were considered to be pathognomic of osteomalacia, but rarely insufficiency-type stress fractures with appearances of Looser zones are described [29, 31].



**Fig. 23.3** Image of Looser zones in osteomalacia in right superior pubic ramus demonstrating all of the characteristics of broad band, minimal callus, transverse and marginal sclerosis in patient with hypophosphataemia due to tumour-induced osteomalacia with elevated FGF23 level. There is also a Looser zone in the right inferior pubic ramus

Bone mineral density (BMD) should be measured at spine, hip and forearm (and whole body for those under 20 years) using dual-energy X-ray absorptiometry. While this does not have any discriminant value in diagnostic terms, BMD is a measure of the risk of fragility fracture and is also a baseline measurement to assess the response to treatment. While correcting vitamin D deficiency in severe cases will result in an improvement in BMD, there is also an irreversible component to the bone loss especially cortical bone that is related to the prolonged phase of SHPT with high bone turnover prior to the onset of the mineralization defect [10]. Hypophosphataemic bone disorders, not having a phase of SHPT, do not have irreversible PTH-mediated bone loss. In some inherited hypophosphataemic disorders, BMD is increased [32].

Bone histology is rarely performed and rarely needed especially with the advance in the above-mentioned biochemical indices. That aside, it is still the gold standard for diagnosing osteomalacia. There are two principal findings: first, accumulation of unmineralized bone matrix called osteoid; second, impaired mineralization as measured using tetracycline-based histomorphometry. It is not sufficient to base a diagnosis on

osteoid indices alone; any condition that increases bone turnover will also increase the surface extent of osteoid. An osteoid seam width  $>12.5 \mu\text{m}$  coupled with a prolonged mineralization lag time  $>100$  days is diagnostic of osteomalacia [11, 33].

## Differential Diagnosis (Table 23.2)

### Intestinal, Hepatic and Renal Diseases

Malabsorption of calcium due to disease must be considered and excluded in all cases. Mucosal disorders most notably celiac disease should be considered. Measurement of antibodies to the enzyme tissue transglutaminase and to endomysium is the best screening test. Diagnosis is confirmed by small bowel histology. Dietary factors should be considered in certain ethnic groups such as Asian immigrants residing in high-latitude countries who ingest unleavened bread, chapati, which impairs calcium absorption. Pancreatic insufficiency and cholestatic liver disease such as primary biliary cirrhosis are less likely to cause vitamin D-related bone disease. Chronic kidney disease in early stages probably has a higher requirement for substrate vitamin D due to progressive impairment in  $1\alpha$ -hydroxylase; at later stages it may manifest with osteomalacia but it is a mixed bone disease including osteitis fibrosa cystica, adynamic bone disease and osteosclerosis.

### Hypophosphataemic Bone Disease (Table 23.3)

Chronic hypophosphataemia also causes rickets and osteomalacia. Chronic hypophosphataemia is usually due to a sustained increase in renal phosphorus excretion, but may also be a consequence of impaired absorption and intake. FGF23 regulates renal phosphorus handling by reducing the expression of sodium–phosphorus cotransporters, and it inhibits  $1\alpha$ -hydroxylase activity. Hypophosphataemic bone disease is now divided into two categories: FGF23-mediated and non-FGF23 mediated [32].

**Table 23.3** Differential Diagnosis of Causes of Rickets and Osteomalacia

1. Vitamin D-related
(a) Privational vitamin D deficiency (combined sun-deprivation and inadequate oral intake)
(b) Disease-specific
• Malabsorption
– Mucosal disorders such as celiac disease
– Pancreatic insufficiency
– Post-gastrectomy
– Gastric bypass
• Primary biliary cirrhosis
• Chronic kidney disease
(c) Inherited
• $1\alpha$ -hydroxylase deficiency (pseudo-vitamin D deficiency)
• Vitamin D receptor defect (hereditary vitamin D resistant rickets)
2. Deficient calcium intake coupled with high phytate intake
(a) In Africa and India, and in Asian immigrants
3. Hypophosphataemic bone disease due to renal phosphorus wasting
(a) FGF23-mediated
• Inherited
– X-linked hypophosphataemia
– Autosomal dominant hypophosphataemic disease
– Autosomal recessive hypophosphataemic disease
• Acquired
– Tumour induced osteomalacia
– Post renal transplant hypophosphataemia
(b) Non-FGF23-mediated
• Fanconi's syndrome
– Drug induced:
Oral iron chelators
Antiretrovirals

See Imel (ref. [12]) and Lips (ref. [14]) for more details

In childhood, the commonest cause of inherited renal phosphorus wasting is X-linked hypophosphataemia due to inactivating mutations in the PHEX gene that is associated with increased bone expression of FGF23 (OMIM 307800). In adulthood, mesenchymal tumours of mixed connective tissue type that produce an excess of FGF23 higher than seen in the inherited conditions leads to severe tumour-induced osteomalacia (TIO). A number of drugs enhance renal excretion of phosphorus resulting in non-FGF23-

mediated rickets or osteomalacia. Of recent interest is the effect of oral iron chelators for treating iron overload on renal phosphorus handling; they cause phosphaturia without increasing FGF23 and lead to both rickets and osteomalacia [34].

Diagnosis of renal phosphorus wasting is straightforward, but it requires measurement of the renal tubular maximum reabsorption of phosphorus per unit of glomerular filtrate:  $TmPO_4/GFR$ . This is conducted by collecting a timed fasting urine and simultaneous blood sample for estimation of phosphorus and creatinine in both serum and urine, and then by calculating  $TmPO_4/GFR$  according to a nomogram or an equation [35]. Hypophosphataemia with a low  $TmPO_4/GFR$  in the absence of hypocalcaemia gives a diagnosis of renal phosphorus wasting. Serum  $1,25(OH)_2D$  levels should be inappropriately low. FGF23 levels can now be measured in specialized laboratories. In childhood, genetic testing for the known mutations should be conducted. In adult patients, acquired causes should be sought including TIO but some of the inherited forms may not present until later in life [32].

## Rare Conditions

A number of conditions may mimic privational vitamin D deficiency. In childhood rare congenital disorders in the metabolism and action of vitamin D should be considered such as: non-functioning 25-hydroxylase (OMIM 600081), non-functioning  $1\alpha$ -hydroxylase called pseudo-vitamin D deficiency (vitamin D-dependent rickets type 1, OMIM 264700) and non-functioning vitamin D receptor called hereditary 1,25-dihydroxyvitamin-D-resistant rickets (HVDRR, or vitamin D-dependent rickets type 2, OMIM 277440) [36]. These conditions are extremely rare and should only be considered in cases where there is failure to respond to standard intervention (see below).

Calcium deficiency of a severe degree, alone, is now considered to be a cause of rickets that is consistent with the known interdependence of calcium and vitamin D. This has been reported in African children in Nigeria and South Africa who

have abundant exposure to sunlight but have extremely low dietary calcium intakes at less than about 200 mg daily on a sustained basis. Intake of foods high in phytate and oxalate that chelate calcium may be confounding factors [30]. Similarly, in India where calcium intake is very low and phytate intake is high rickets and osteomalacia is reported, despite with what would be considered satisfactory vitamin D status in regions where calcium intake is much higher [37, 38].

Hypophosphatasia (OMIM 146300) is a rare heritable form of rickets and osteomalacia that is caused by sub-normal activity of tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). It may manifest in different clinical forms: perinatally with a fatal form, in infancy with severe rickets, in childhood with milder bone disease accompanied by premature loss of teeth, and in adulthood with poorly healing metatarsal stress fractures. Serum total alkaline phosphatase is low, while calcium, phosphorus, 25OHD and PTH levels are normal. In fact there is a tendency to hypercalcaemia and hyperphosphataemia. So standard treatment for rickets should be avoided; in fact a restricted calcium intake may be needed to avoid hypercalcaemia [39].

Chronic metabolic acidosis can cause a mineralization defect. This is seen with renal tubular acidosis as a consequence of renal bicarbonate-wasting. This is a direct effect of the acidotic state on bone, which functions as part of the buffering response in the body. Urinary diversion techniques may result in chronic metabolic acidosis, especially uretero-sigmoidostomy that was performed in the past and to a lesser extent the extant procedure of uretero-ileostomy. A simple indicant on routine testing is the presence of a normal anion gap metabolic acidosis accompanied by hyperchloremia.

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## Present and Future Therapies

### Vitamin D and Calcium Supplementation

Privational vitamin D deficiency is corrected and prevented safely and efficaciously by low-dose

vitamin D supplementation. The intake requirements for both vitamin D and calcium as specified by the recent IOM report should be followed (Table 23.3) [3, 6]. Vitamin D<sub>3</sub> is favoured over D<sub>2</sub> due to the greater potency of the former [12, 40].

The IOM report has made an invaluable contribution to clinical practice (Table 23.1). Foremost, it directs clinician to distinguish between two different at-risk populations: (1) those who are at risk as a consequence of sun-deprivation with resultant inadequate vitamin D synthesis, which includes all those, by definition, with privational vitamin D deficiency worldwide; and (2) those at risk for disease-specific reasons [8]. The former group only need to augment oral intake of vitamin D and calcium as specified by IOM. The latter group require clinical evaluation. For instance, an individual may have a higher intake requirement of both calcium and vitamin D in order to achieve the same optimal level of vitamin D status as the healthy population—the best example being patients with chronic malabsorption. Here, the clinician is guided by the secondary indices, in addition to 25OHD levels, in order to assess the success of supplementation doses of vitamin D and calcium. Alternatively, the patient may have a higher 25OHD threshold for adequacy—the best example being the patient with progressive chronic kidney disease, who needs a higher substrate concentration of 25OHD for activation in the kidney as consequence of declining 1 $\alpha$ -hydroxylase activity. If higher doses of vitamin D are needed, then patients will need frequent monitoring of 25OHD and other indices such as PTH levels both to assess efficacy and to avoid toxicity.

In view of the interdependence of calcium and vitamin D, the adequacy of calcium intake must be considered in all clinical situations of privational vitamin D deficiency [3]. This is particularly important in regions where dietary calcium intake is very low and phytate intake is high [37, 38]. One recent guideline failed to mention at all about ensuring satisfactory calcium intake [41] but instead promoted vitamin D intakes that were threefold to fivefold higher than IOM specified intakes for preventing privational hypovitaminosis D [8, 42].



## High-Dose Vitamin D Therapy

High-dose vitamin D therapy is often advocated both for the treatment and prevention of privational vitamin D deficiency. Suggested doses range from 50,000 to 500,000 units, are administered either orally or intramuscularly, and are prescribed at intervals ranging from once weekly to yearly. As a preventative strategy for at-risk populations, it is often recommended as a means of overcoming poor adherence. Clinicians should be cautious about this approach for a number of reasons: (1) for cases of rickets and osteomalacia, one must understand that one is dealing with a chronic disorder that evolved slowly over a long time, and is not possible to correct acutely at the bone level; (2) one may unwittingly omit to consider calcium supplementation when prescribing a very high dose vitamin D; (3) risk of toxicity. High dose therapy is harmful; it should be considered a pharmacologic agent, and it should not be considered equivalent to an average daily dose [12]. Two recently published high dose trials demonstrated harm unexpectedly in their pre-specified outcomes. One study of elderly over 70 years were assigned to receive placebo or 500,000 D<sub>3</sub> orally once yearly for 5 years to test whether there was a reduction in falls and fractures. There was a significant increase in falls and a trend towards an increase in fractures [43]. Another study of infants aged 1–11 months in Kabul were assigned to receive placebo or 100,000 IU D<sub>3</sub> orally every 3 months for 18 months to test whether it reduced the incidence and severity of pneumonia. No benefit was observed but they recorded a significant excess of repeat episodes of pneumonia, which was a pre-specified secondary outcome [44].

## Activated Vitamin D Analogues

Rather than opting for high dose parent vitamin D in cases of chronic malabsorption, one should consider use of activated vitamin D: 1,25 (OH)<sub>2</sub>D or its monohydroxylated analogue 1 $\alpha$ -hydroxyvitamin D, which is slightly less potent. Usually, the starting dose is about 0.25  $\mu$ g twice daily increasing until resolution of the

biochemical abnormality. Additional calcium supplementation is usually warranted. Parent vitamin D<sub>3</sub> should also be administered in an effort to try and improve vitamin D status both for endocrine and intracrine effects. Careful monitoring of calcium status, both in serum and urine, is advised for patients on activated forms of vitamin D in view of the risk of hypercalcaemia and hypercalciuria.

## Future Therapies

An intractable problem that is rarely encountered in patients with prolonged malabsorption is refractory secondary hyperparathyroidism that persists despite restoring calcium status to normal. In time, these patients progress to autonomous hyperparathyroidism with hypercalcaemia. They tend to have marked increases in bone turnover markers, both resorption and formation, and have accelerated bone loss on densitometry. They may even progress to osteitis fibrosa cystica. One cannot increase the dose of activated forms of vitamin D because of the risk of hypercalcaemia. Some patients may need total parathyroidectomy with remnant implantation. A new alternative is to use a calcimimetic agent such as Cinacalcet. This is licensed for use in the treatment of primary hyperparathyroidism and secondary hyperparathyroidism in the setting of chronic kidney disease. Use in the setting of refractory secondary hyperparathyroidism would be off-label. Early introduction of calcimimetic therapy may halt the progress towards requiring parathyroid surgery.

## Conclusion

Privational vitamin D deficiency is common in groups at risk of sun-deprivation. It is straight forward to investigate using standard biochemical tests. It is effectively and safely corrected by following IOM specified intakes. More severe and refractory cases should be investigated for other causes of vitamin D-related deficiency and for hypophosphataemic bone disease; these conditions are likely to need expert evaluation and pharmacologic intervention with regular supervision of response to intervention.

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## Introduction

Osteoporosis is a disorder characterized by low bone mass, with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fractures. It is the most common of all osteoid-metabolic disorders and represents a major public health problem worldwide, affecting one in every three women aged 50 and over. Its incidence is most likely associated with the aging of the world's population.

Studies in the USA such as the NHANES III study (Third National Health and Nutritional Examination Survey) have confirmed an elevated occurrence of osteoporosis, with prevalence in the femoral neck of patients over 50 years of age,

showing that 20 % of women of Caucasian and Hispanic origin, 7 % of black women, and 7 % of all men are affected [1], which corresponds to around ten million people, 80 % of whom are women. Studies indicate that half of all postmenopausal women will have an osteoporotic fracture during their lifetime, with potential consequences that include short-term and long-term morbidity, not to mention the economic aspects involved. Costs related to osteoporosis in 2005 reached approximately \$17 billion, and could double or triple by 2040. Although medical therapy can reduce the risk of fractures, and is cost-effective, osteoporosis often goes undiagnosed and untreated. The U.S. Preventive Services Task Force (USPSTF) therefore recommends that all women 65 and over should be routinely examined [2].

In Brazil there is no concrete data on the occurrence of osteoporotic fractures. It is estimated that around 10 million people in the country have osteoporosis, and 2.4 million suffer from some type of fracture each year. A study in Recife that evaluated 657 women over 50 years of age found that 29 % of them demonstrated the presence of osteoporosis in the lumbar spine, and 19 % in the femoral neck, with an increased prevalence accompanying the advancement of age [3].

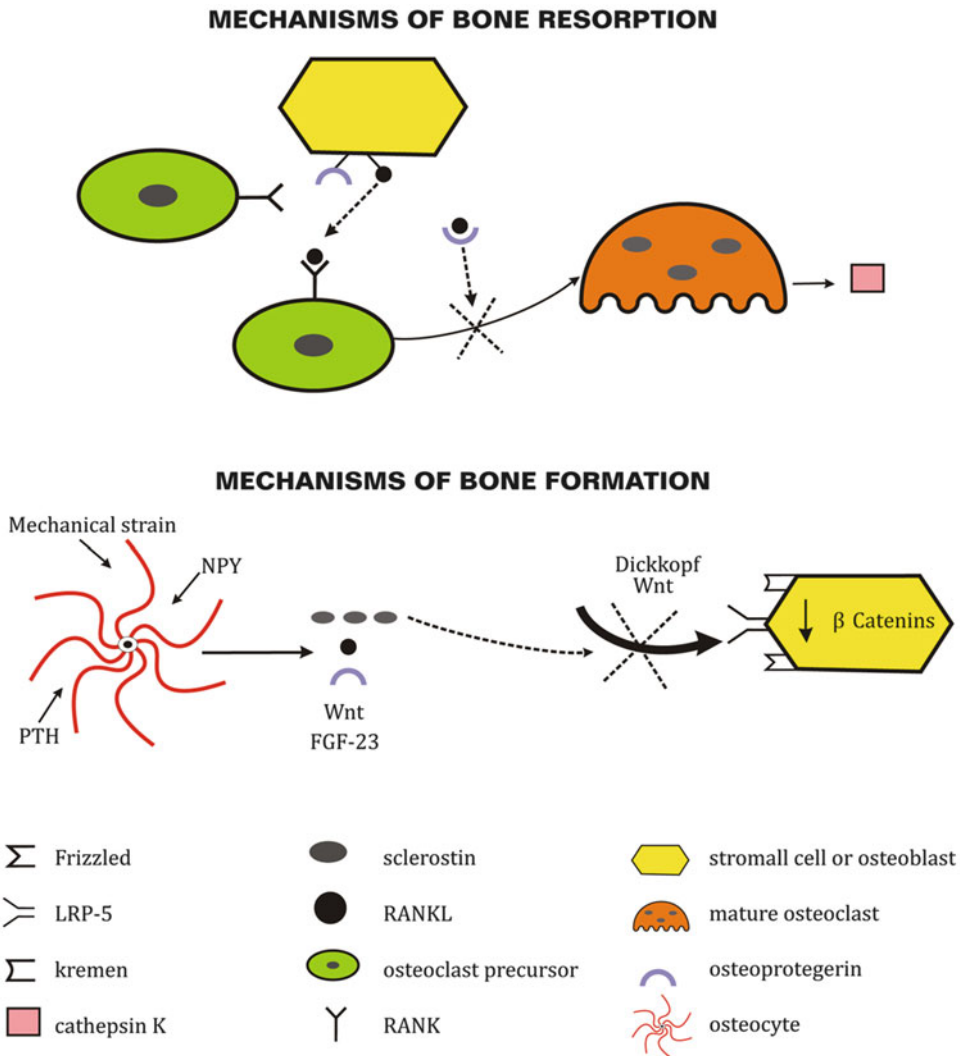
The pathophysiology of osteoporosis is shown in Figs. 24.1 and 24.2. It is important to recognize the problem, along with its risk factors and consequences in order to decrease morbidity, mortality, and the costs associated with the disease.

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**Fig. 24.1** Mechanisms of bone resorption. The stromal cells or osteoblast releases RANKL and osteoprotegerin. RANKL will bind to RANK on the surface of the osteoclast precursor, leading to fusion and differentiation of this

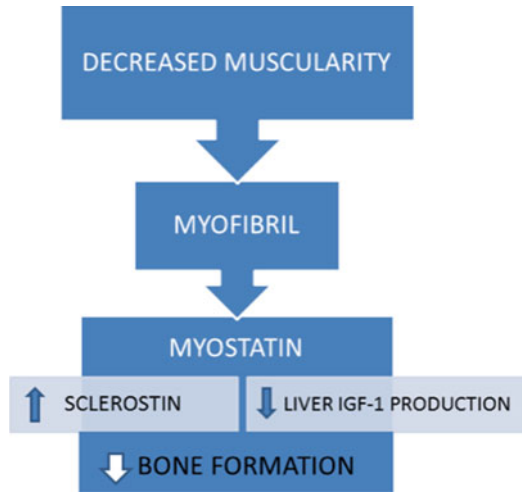
cell into mature osteoclasts, which in turn release cathepsin K. When there is increased production of osteoprotegerin, such as in estrogen deficiency, the osteoprotegerin binds to RANKL inhibiting the formation of mature osteoclast

## Risk Factors

Osteoporosis is a multifactorial disease, consisting of some aspects that are potentially modifiable, and others that are not. Factors that are genetic, racial, and anthropometric, along with those related to body composition, bone density, diet, physical activity, and other lifestyle factors, are important elements in the predisposition to and development of osteoporosis.

The two major risk determinants for developing osteoporosis are peak bone mass and rate of bone loss. Risk factors that influence these determinants should be evaluated in all postmenopausal women in order to properly estimate the threat of fractures, exclude secondary causes of osteoporosis, identify modifiable risk factors, and determine the appropriate drug therapy for each case [4].

The main risk factors for osteoporosis are listed in Table 24.1.



**Fig. 24.2** Mechanisms of bone formation. The osteocyte, under the action of PTH, mechanical strain, and NPY, releases sclerostin, which will block the binding of proteins Wnt and Dickkopf to osteoblast receptors, especially the LRP-5

**Table 24.1** Risk factors for osteoporosis

Family history of osteoporosis	Cushing syndrome, and use of corticosteroids
Advancement of age	Chronic renal failure
Female gender	Celiac disease
Sedentary lifestyle	Hyperthyroidism
Malnutrition	Primary hyperparathyroidism
Low calcium and vitamin D intake	Multiple myeloma
Diabetes mellitus <sup>a</sup>	Time of menopause
Smoking	Low body weight
Alcoholism	Obesity <sup>b</sup>
Personal history of fractures	Deficiency of GH and IGF-1
Delayed puberty and/or hypogonadism	Vitamin D deficiency
Prolonged immobilization	Depression

Data from ref. [4]

<sup>a</sup>Diabetics show an increase in sclerostin, and a decrease in bone mineral density

<sup>b</sup>Obesity increases the risk for some types of fractures

## FRAX

FRAX™ is a tool available online (<http://www.shef.ac.uk/FRAX/index.htm>) which was developed by the World Health Organization. It is employed to gather independent risk factors for osteoporotic fractures involving individuals over 50 years of age, in order to quantify the probability of fracture of the femoral neck or other major osteoporotic fractures (vertebral, hip, forearm, and humerus) over the following 10 years.

The variables considered include gender, age, BMI, personal history of fractures after the age of 40, family history of hip fractures, smoking, excessive alcohol consumption, rheumatoid arthritis, use of glucose-corticoids, or other secondary causes of osteoporosis [5].

Using population samples from Europe, North America, Asia, and Australia, country-specific data was compiled, allowing calculations based on regional differences. When FRAX is associated with bone mineral density (BMD) testing, it

is a more useful tool for predicting fracture risk than the use of either FRAX or BMD alone.

Although its use is not routinely indicated for patients who are already being treated for osteoporosis, a recent study demonstrated that FRAX may be a useful tool for assessing fracture risk in these patients, pointing to the need to either continue or discontinue medication [6].

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## Diagnosis

### Clinical History and Physical Examination

Through a clinical history and thorough physical examinations it is possible to detect secondary causes of osteoporosis and risk factors for osteoporosis. In the clinical evaluation of the patient, weight, height, family history of osteoporosis, age, race, nutritional status, calcium and vitamin D intake, thoracic–lumbar pain (chronic or acute), decreased stature, chest deformities, medication use (current and previous), menstrual cycles, time of menopause, history of fractures, and lifestyle habits (smoking, alcohol consumption, and physical activity) should all be taken into consideration.

Most patients with osteoporosis are asymptomatic until the onset of clinical fractures. Vertebral fractures can result in loss of height and/or kyphosis, and local pain, due mainly to the shortening and contracture of the para-spinal musculature caused by the reduction of vertebral height [7]. However, most vertebral microfractures are asymptomatic.

Postmenopausal women should also be questioned regarding clinical factors associated with an increased risk of falls, including history of falls, fainting, muscle weakness, problems with coordination and balance, difficulty walking, arthritis in the lower limbs, peripheral neuropathy, and decreased visual acuity.

### Laboratory Evaluation

Laboratory tests are important, primarily to exclude secondary causes of osteoporosis. The

initial evaluation should include the following: CBC, VSH, 24-h calciuria, calcium, albumin, phosphorus, transaminases, alkaline phosphatase, protein electrophoresis, renal function, thyroid function, PTH, and 25 (OH) vitamin D. If any secondary cause is clinically suspected and/or bone loss greater than expected for the age, investigations should be extended to include cortisol after 1 mg of dexamethasone, anti-gliadin and anti-endomysial antibodies, bone marrow study, serum iron, and ferritin (for suspected hemochromatosis).

### Bone Markers

Bone markers are substances released during bone remodeling processes, which can be assayed in serum or urine, and provide dynamic assessment of the activity of the skeleton.

Markers for resorption as well as formation may be utilized (Table 24.2).

These markers should not be used single-handedly for the diagnosis of osteoporosis, nor even to determine which patients require treatment, but they can be useful in predicting bone loss. Studies show that the higher the level of markers, the greater the decrease in bone mass in subsequent years if treatment is not instituted.

The best and most validated use of bone markers is to monitor treatment. Anti-resorptive therapy is associated with the reduction of all resorption markers after 3 months, remaining at these reduced levels while the patient is in treatment. In cases where the response is inadequate and treatment compliance by the patient has been confirmed, the possibility of changing medication or increasing the dosage should be evaluated.

### Imaging

#### Plain Radiography

Plain radiographs demonstrate low sensitivity for the diagnosis of osteoporosis because they show an alteration only when a bone loss of at least 30 % already exists. They can be useful for diagnosing fractures, or specialized diagnosis

**Table 24.2** Bone formation and resorption markers

Formation markers	Resorption markers
Alkaline phosphatase	Telopeptides of collagen cross-links
Osteocalcin	Amino-terminal amino-NTX (N-telopeptide)
Pro-peptides of type I collagen	Carboxy-terminal—CTX (C-telopeptide)
– Amino-terminal (PINP)	Pyridinolines
– Carboxy-terminal (PICP)	Hydroxyproline
– Osteocalcin (OCN)	Tartrate-resistant phosphatase acid

involving other diseases that can affect bone, such as multiple myeloma, osteomalacia, and bone metastases.

Since most vertebral fractures are asymptomatic, several techniques have been studied with the aim of objectively recognizing subclinical vertebral deformities by measuring the height of the vertebral bodies (called morph-metric fractures). The semi-quantitative score permits a percentage differential evaluation of the anterior, middle and posterior heights of the vertebral bodies, in order to effectively assess the severity of vertebral fractures [8].

- 0 Degree—No fracture exists
- 1st Degree—Mild fracture—reduction ranging from 20 to 25 % of the vertebral height
- 2nd Degree—Moderate fracture—reduction ranging from 25 to 40 % of the vertebral height
- 3rd Degree—Severe fracture—reduction > 40 % of the vertebral height

### Bone Densitometry

Osteoporosis can be diagnosed before the onset of clinical fractures by means of noninvasive methods for determining bone mineral density (BMD), which is the best single predictor of fracture risk [9]. The most accurate noninvasive method is bone densitometry, and the most widely used measure of absorption is dual energy X-ray absorptiometry (DXA), which measures the area density (grams of mineral per square centimeter of bone;  $g/cm^2$ ). It can be used at central (lumbar spine, and hip) or peripheral (distal radius, heel, and phalanges) sites; however, only central sites are used for diagnosis and monitoring response to treatment.

The World Health Organization (WHO) has defined the diagnosis of low bone mass and

**Table 24.3** Definition of osteoporosis by the WHO criteria

WHO classification	T-score
Normal	To $-1.0$ DP
Osteopenia	$-1.0$ to $-2.5$ DP
Osteoporosis	$< -2.5$ DP

Data from ref. [10]

osteoporosis, based on the number of standard deviations (SD) below mean BMD detected in normal young adults of the same sex (T-score) [10] (Table 24.3).

The BMD of osteoporotic patients may also be compared with that of a population of corresponding age (Z-score). A Z-score below  $-2.0$  SD is considered below the expected range for the age group [11], and in these cases should be investigated for secondary causes of osteoporosis.

Since all postmenopausal women are at risk of developing osteoporosis, it would be ideal to evaluate the BMD of all of them. As a way of limiting costs, the International Society of Clinical Densitometry (ISCD) suggests screening for osteoporosis in women over 65 years of age; those with a history of fractures after minimal or no trauma; in early menopause; with prolonged use of corticosteroids; osteopenia evidenced by plain radiography; a maternal history of osteoporosis or fracture, loss of height or thoracic kyphosis; underweight ( $BMI < 19$ ), secondary causes; and the use of medications associated with bone loss [11].

### Quantitative Computerized Tomography

This is a technique that measures volumetric density ( $g/cm^3$ ) at the lumbar spine and peripheral sites using specialized software and standard



computerized tomography equipment. It is able to distinguish cortical and trabecular bone compartments and predict fracture risk, as well as DXA, but has a high cost along with limited availability and increased radiation exposure, being used mainly in clinical research.

### **Ultrasonography**

This evaluates the heel bone and the proximal tibia, is practical and inexpensive, and is useful as a method for screening the population at risk for osteoporosis.

### **Bone Quality**

The concept of bone quality has been widely used to justify the occurrence of clinical events not explained by the evaluation of BMD alone. Bone quality takes into consideration the composition and structure of bone, contributing to bone strength regardless of density. Several factors interact to form bone quality, such as bone turnover, geometry, micro-architecture, mineralization; micro-aggressions, and components of the mineral and bone matrix [12].

The evaluation of bone turnover may be conducted through bone marker evaluation and biopsies performed on bone marked with tetracycline [13]. New techniques for bone quality assessment have been developed, such as high-resolution magnetic resonance imaging, and high-resolution peripheral quantitative computerized tomography. However, these costly techniques have yet to become readily available.

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## **Treatment**

### **Indication**

Many guidelines have been published concerning the management of osteoporosis, in which treatment decisions are based primarily on the results of BMD in combination with patient characteristics.

The FRAX approach developed by the WHO plays a crucial role in guiding treatment recommendations for the management of osteoporosis [14].

The National Osteoporosis Foundation (NOF) recommends treatment of postmenopausal women (and men 50 years or older) with a history of vertebral or hip fracture or osteoporosis based on the measurement of BMD (T score of  $-2.5$  or less), as well as postmenopausal women with osteopenia, (BMD T score between  $-1.0$  and  $-2.5$ ) associated with a 3 % or greater likelihood of hip fracture within 10 years, or a 20 % or greater likelihood of osteoporotic fracture calculated by the FRAX approach [15].

The ideal optimal duration of pharmacological treatment for postmenopausal osteoporosis remains controversial. The decision to continue or discontinue therapy should be based on the history and fracture risk, balanced with the risks and benefits of the medication.

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## **Non-pharmacological Treatment**

There are three main components in the non-pharmacologic therapy of osteoporosis: diet, exercise, and the cessation of smoking. In addition, the patient should also avoid drugs that increase bone loss, such as glucose-corticoids.

### **Calcium/Vitamin D**

An optimum diet for the treatment of osteoporosis includes an adequate amount of calories (to prevent malnutrition), along with calcium and vitamin D. Postmenopausal women should have an adequate intake of elemental calcium in divided doses, totaling 1,000–1,200 mg/day [16].

A recent study with 31,022 patients showed that vitamin D supplementation leads to a less than significant reduction of 10 % in the risk of hip fracture (hazard ratio, HR 0.90, CI 95 % 0.80–1.01) and a 7 % reduction in the risk of non-vertebral fractures (HR 0.93, CI 95 % 0.87–0.99) when compared with a control group. When intake levels were differentiated, fracture risk reduction was demonstrated only at the highest level of intake (median, 800 IU per day), with a 30 % reduction in the risk of

hip fracture (HR 0.70; CI 95 % 0.58–0.86) and a 14 % reduction in the risk of any type of non-vertebral fracture (HR 0.86, CI 95 % 0.76–0.96) [17].

## Physical Exercise

Women with osteoporosis should perform physical exercise for at least 30 min three times a week, since exercise has been associated with a reduced risk of hip fracture in older women [18].

A recent meta-analysis of 43 random clinical trials with 4,320 postmenopausal women showed a significant positive effect of exercise on the BMD of the lumbar spine and trochanter. The most effective type of exercise for femoral neck BMD was resistance training using progressive force. A combined program that included more than one type of exercise was the most efficient for lumbar spine BMD [19].

## Pharmacological Treatment

There are several medications that can be used in the treatment of osteoporosis. The main medications employed are reviewed below (Table 24.4).

### Estrogens

Several placebo-controlled, randomized studies, including the WHI study and the postmenopausal estrogen/progesterone intervention (PEPI) study have established that decreases in BMD are attenuated by estrogen, resulting in a lower risk of fracture [20, 21].

In the WHI study, estrogen-progestin therapy was associated with significant reductions in hip fractures (OR 0.7, CI 95 % 0.4–1.0 unadjusted; less than five hip fractures per 10,000 person-years), along with vertebral and other osteoporotic fractures (OR 0.7, CI 95 % 0.4–1.0 unadjusted, and OR 0.8, CI 95 % 0.7–0.9, respectively) [20]. A similar risk reduction for hip fractures was shown using estrogens alone (OR 0.61,

**Table 24.4** Reduction in fracture incidence

Drugs	Vertebral fracture	Non-vertebral fracture	Hip fracture
Zoledronate	+	+	+
Risendronate	+	+	+
Alendronate	+	+	+
Strontium	+	+	+ <sup>a</sup>
Estrogen	+	+	+
Teriparatide	+	+	–
Calcitriol	+	–	–
Ibandronate	+	+	+ <sup>a</sup>
Raloxifen	+	–	–
PTH 1-84	+	–	–
Calcitonin	+	–	–
Denosumab	+	+	+

Data from refs. [28, 40–43, 46–48, 55, 64]

<sup>a</sup>Post hoc subgroup analysis

95 % CI 0.41–0.91), as were reductions for vertebral fractures (OR 0.62, 95 % CI 0.42–0.93) [22].

In a forthcoming sample study, the Million Women Study, current users in postmenopausal therapy were shown to have a significantly lower risk of any fracture when compared to nonusers (RR 0.62, CI 95 % 0.58–0.66) [23].

The coadministration of a progestogen, cyclically or continuously, to prevent endometrial hyperplasia does not impair the beneficial effects of estrogen [21].

However, estrogen-progestin therapy is no longer a front-line approach for the treatment of osteoporosis in postmenopausal women, owing to the increased risk of breast cancer, venous thromboembolism, stroke, and perhaps also coronary disease [20].

### Tibolone

Tibolone is a synthetic steroid whose metabolites have estrogenic, androgenic, and progestogenic properties. It is used to treat osteoporosis in some countries. In postmenopausal women with osteoporosis, tibolone use has produced a 5–12 % increase in lumbar spine BMD within 2 years. However, despite the fact that the LIFT study has reported a reduced risk of vertebral and

non-vertebral fractures through the use of tibolone, it was stopped at an early stage because of the unacceptable risk of cerebral stroke [24]. This casts doubt on the drug's safety.

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## Calcitonin

Using calcitonin for the treatment of osteoporosis, a study that included 5 years of follow-up with 1,255 women with T-scores of less than -2 (lumbar spine and at least one vertebral fracture), randomly assigned either a placebo or doses of 100, 200 or 400 IU/day of intranasal calcitonin. A small and inconsistent beneficial effect on the vertebral BMD from nasal calcitonin treatment was found, and included a reduction in the risk of vertebral fractures [25].

Data on the effect of calcitonin in locations other than the spinal column are conflicting.

A recent meta-analysis with heterogeneous results, using a limited number of patients, showed calcitonin to be of benefit for the short-term relief of acute pain (less than 10 days) in patients who have suffered a vertebral fracture. In contrast, calcitonin has not proved to be effective for patients with chronic pain (over 3 months) [26].

## SERMs (Selective Modulators of Estrogen Receptors)

Selective modulators of estrogen receptors (SERMs) bind with high affinity to the estrogen receptor, having agonist and antagonist properties that vary, depending on the target organ.

Raloxifene is a SERM effective in the treatment of established osteoporosis, which increases BMD in both the lumbar spine and the hip [27–30], and reduces the risk of vertebral fractures [28]. It also appears to reduce the risk of breast cancer without stimulating endometrial hyperplasia or vaginal bleeding, but does seem to increase the risk of venous thromboembolism (VTE) [27]. In addition, there are studies that refer to an increased risk of fatal cardiovascular accidents (CVA) [27, 31]. Although serum concentrations of low density lipoprotein (LDL)

cholesterol and total cholesterol decrease, there seems to be no change in the risk of coronary cardiac disease [27].

However, despite the fact that raloxifene reduces vertebral fracture risk in postmenopausal women, it is not clear whether there is a reduction in non-vertebral fractures, and therefore seems to be a less potent anti-resorptive agent than alendronate or estrogen [32, 33].

Moreover, unlike the bisphosphonates, SERMs do not appear to have a long-lasting effect on the skeleton, and have no residual beneficial effects on BMD after discontinuation of treatment.

In a recent study, raloxifene was shown to decrease the mortality rate from all causes, mainly due to the reduction in non-cardiovascular and non-oncological deaths owing to a mechanism that has yet to be clarified [34].

Tamoxifen, a SERM used most commonly for the treatment of estrogen-dependent breast cancer, also affords some protection against bone loss in postmenopausal women, and can be used to treat osteoporosis by reducing fracture rates [35].

Bazedoxifene has also decreased the incidence of new vertebral fractures, but not non-vertebral ones, with common adverse effects that include hot flashes, cramps, low rates of endometrial hyperplasia, cancer, polyps, and slightly higher rates of DVT, effects somewhat similar to those of raloxifene [36].

Lasofloxifene, like raloxifene, reduces the incidence of vertebral fractures, but also increases the risk of thromboembolic events, hot flushes, and cramps in the legs. After 5 years of use, lasofloxifene has also been shown to be associated with a decrease in non-vertebral fractures, an effect that raloxifene has not shown. However, none of the SERMs reduce the risk of hip fractures [37].

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## Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate in which the oxygen bridge is replaced by a carbon atom [38]. They suppress bone resorption mediated by osteoclasts through a mechanism different from other anti-resorptive

agents, binding to hydroxyapatite on bone surfaces, particularly those undergoing active resorption. When the osteoclasts begin to reabsorb bone that is impregnated with bisphosphonate, the bisphosphonate released during resorption impairs the ability of osteoclasts to form the wrinkled edge needed to adhere to the bone surface, thereby producing the protons required to continue bone resorption. In addition, they also reduce the activity of the osteoclasts, compromising the development of osteoclast progenitors, along with the recruitment and promotion of apoptosis of the osteoclasts. There also appears to be a beneficial effect on the osteoblasts [39].

Bisphosphonates can be administered orally (alendronate, risedronate, ibandronate) or intravenously (zoledronic acid at a dose of 5 mg every 12 months, and ibandronate in a dose of 3 mg every 3 months) [38, 40–43]. They avidly bind to bone minerals, especially to trabecular bone, with a high degree of specificity [44]. However, oral absorption is low (0.6–1.5 % of the administered dose). Approximately 40–60 % of the dose is distributed in the bone, the remainder being excreted unchanged in the urine without substantial metabolism [38].

Oral bisphosphonates should be taken once a week after fasting, (alendronate in a dose of 70 mg, and risedronate in a 150 mg dose), once a month (ibandronate in a dose of 70 mg or risedronate in a 150 mg dose), or on 2 consecutive days, once a month (risedronate in a dose of 75 mg). The patient must remain upright for at least 30 min after taking the drug in order to minimize gastroesophageal reflux and enhance absorption. Afterwards, food, medications, and other liquids should be avoided for at least 30–45 min [40].

Oral and intravenous bisphosphonates are contraindicated in patients who have had previous allergic reactions to any bisphosphonate, or creatinine clearance estimated at 35 ml/min or less, vitamin D deficiency (serum 25 hydroxyvitamin D less than 30 ng/ml), osteomalacia or hypocalcemia [40].

Oral bisphosphonates are also contraindicated in patients with impaired swallowing, or esophageal disorders such as achalasia, esophageal varices, severe gastroesophageal reflux, or those who

are unable to sit for at least 30 min after taking the medication [40].

An acute phase reaction (fever, myalgia, bone pain and weakness) occurs in 20 % of patients after an initial intravenous infusion of bisphosphonate and, in a very small number of patients, during oral therapy. Erosive esophagitis, ulceration, and bleeding have been associated with daily oral therapy using alendronate or risedronate, but seldom occur with the current regimes (not daily). Heartburn, chest pain, hoarseness, and irritation of the vocal cords can occur with weekly (alendronate or risedronate) or monthly therapy (ibandronate or risedronate) [40].

Osteonecrosis of the jaw is a rare but serious complication of long-term therapy that can appear spontaneously, or after dental surgery. Case reports suggest that atypical fractures of the femur (subtrochanteric and mid-diaphyseal portions) may also occur during prolonged therapy [40, 45].

There are no known interactions between bisphosphonates and other drugs. Evidence of treatment failure with patients adhering properly to a treatment regime indicates the need to change from orally administered bisphosphonate to intravenous zoledronic or another class of drugs, such as anabolic agents (e.g., teriparatide) [40].

Bisphosphonates suppress biochemical indices of bone resorption by around 50 % in a month, significantly reducing the incidence of vertebral, and non-vertebral fractures, including femoral fractures in patients with osteoporosis within a few months after the start of therapy [44].

BMD increases modestly by around 2–6 % during the first year of treatment. In the lumbar spine, it continues to increase slowly for several years, but in the femur, it reaches a plateau after about 2 years. Therapy preserves bone, but does not increase bone volume, or restore the bone structure [44].

In the Fracture Intervention Trial (FIT) [41], postmenopausal women with a high risk of fracture, a low BMD in the femoral neck, and at least one vertebral fracture, the alendronate group showed fewer new vertebral fractures ( $p=0.001$ ) and new hip fractures ( $p=0.05$ ), when compared with the placebo group [40, 41].

In the vertebral efficacy study with risedronate therapy (VERT) [42], 2,458 postmenopausal

**Table 24.5** Reduction in vertebral fracture incidence at pivot trials

Study	Increase in BMD	Reduction in vertebral Fx <sup>a</sup> (RRR)	Baseline vertebral Fx <sup>a</sup>	ARR/NNT (3 yr) <sup>a</sup>	Drug
FIT II	8.3 %	44 %	0 %	1.7 %/59	Alendronate
FIT I	7.9 %	47 %	100 %	7 %/15	Alendronate
VERTMN	7.1 %	39 %	100 %	10 %/10	Risedronate
VERTNA	5.4 %	31 %	100 %	5 %/20	Risedronate
MORE	2.6 %	35 %	37 %	6.5 %/16	Raloxifen
BONE	6.0 %	52 %	100 %	4.9 %/21	Ibandronate
FPT	14 %	65 %	100 %	9 %/12	Teriparatide
HORIZON	7.0 %	70 %	60 %	7.6 %/14	Zoledronate
SOTI	14 %	41 %	100 %	11 %/9	Strontium Ranelate
FREEDOM	10 %	68 %	23 %	4.8 %/21	Denosumab

Data from refs. [28, 43, 46, 48, 54, 64]

<sup>a</sup>Fx fracture, RRR relative reduction risk, ARR absolute reduction risk, NNT number needed to treat

women with at least one vertebral fracture, and lumbar spine T scores of  $-2.0$  or less, the risedronate group had a lower rate of new vertebral fractures after 3 years when compared to the placebo group. In a subsequent trial, risedronate also proved to be effective in reducing the rate of hip fractures [40, 42].

In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly study (HORIZON clinical trials), 7,765 postmenopausal women suffering from osteoporosis were treated with zoledronic acid (5 mg once a year for 3 years). When compared to the placebo group, they showed a significant reduction in the absolute rate of new vertebral fractures as assessed by radiography, and also of new hip fractures [40, 44, 46] (Table 24.5).

Other placebo-controlled and randomized oral bisphosphonate studies, including with ibandronate, clodronate, and etidronate, have also shown the efficacy of these medications in reducing the risk of new vertebral fractures. However, these trials were not shown to have the statistical capacity to demonstrate efficacy in the treatment of hip fractures, which makes them less useful clinically. Pamidronate has been used to treat a variety of bone diseases in children and adults, but no studies have evaluated the efficacy of the medication with sufficient capacity to treat hip fractures in postmenopausal women with osteoporose [40].

The optimal duration for bisphosphonate therapy remains unclear. However, based on available data, it appears likely that discontinuation of therapy after 5 years, at least as a temporary pause for 1–2 years, is not harmful, and may indeed be beneficial. It could be especially appropriate in patients with an only slightly low BMD, which would imply a lower risk of fractures if bone loss does occur when the person is not receiving treatment [40].

In addition, concern about the occurrence of atypical subtrochanteric fractures and osteonecrosis of the jaw during prolonged bisphosphonate therapy has led the Food and Drug Administration (FDA) to reassess the efficacy of bisphosphonate therapy, with extension of the FLEX study involving alendronate for 5 more years, and the HORIZON study with zoledronic acid for 3 more years [47].

This analysis by the FDA revealed little benefit from continued treatment with bisphosphonates beyond 5 years in the final endpoint comprising all vertebral and non-vertebral fractures, but was consistent in showing significant reductions in vertebral fracture risk with continued bisphosphonate treatment, with no overall reduction in the rate of non-vertebral fractures [47].

Observational studies have shown a greater loss of bone after discontinuation of therapy with risedronate, but there is no data with ibandronate.

It is therefore believed that recommendations concerning discontinuation should be limited to alendronate and zoledronic acid [47].

On current evidence, it can be concluded that with patients showing low bone mineral density in the femoral neck (T score below  $-2.5$ ) after 3–5 years of treatment there is an increased risk of vertebral fractures, and it would thus seem more beneficial to continue with bisphosphonates. The same applies to patients with existing vertebral fractures and a slightly higher T Score, but not above  $-2.0$ . In cases involving patients with a T score above  $-2.0$  in the femoral neck, there is a low risk of vertebral fractures, and they are unlikely to benefit from continued treatment [47].

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## Denosumab

Denosumab (Prolia<sup>®</sup>) is an IgG2 monoclonal antibody that, similarly to the action of osteoprotegerin (OPG), binds with high affinity and specificity to RANK L, preventing it from activating its receptor (RANK) on the surface of osteoclasts and their precursors. The prevention of the RANKL/RANK interaction inhibits the formation, function, and survival of osteoclasts, thereby decreasing bone resorption.

Denosumab is administered via a subcutaneous injection (SC) of 60 mg every 6 months, requiring no dose adjustment for renal function. Its safety and tolerability have been demonstrated in clinical studies of up to 8 years' duration [48, 49].

Studies have demonstrated that a single dose of denosumab leads to significant suppression of bone turnover. Bone reabsorption markers decrease substantially within 12–24 h after administration of the medication, and this effect has been shown to be reversible upon its clearance [50].

The FREEDOM study (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months) was a phase III, double-blind, placebo-controlled study lasting 36 months, and was designed to analyze the effectiveness of denosumab in reducing vertebral fractures in postmenopausal women. Over 3 years, it evaluated 7,808 women with a mean age of 72.3 years, T-scores  $<-2.5$  and demonstrated a significant

reduction in the incidence of new vertebral fractures, non-vertebral fractures, and hip fractures, along with a significantly increased BMD in the lumbar spine (9.2 %) and total hip (6.0 %) when compared to the placebo group ( $p < 0.001$ ). Furthermore, a substudy of FREEDOM ( $n = 160$ ) showed that the medication reduces markers for bone remodeling (sCTX and sPINP) within the first month [48].

The DECIDE study (Determining Efficacy: Comparison of Initiating Denosumab versus Alendronate) was a phase III, multicenter, randomized, double-blind study that compared the efficacy and safety of treatment with denosumab vs. alendronate for 12 months in postmenopausal women with T-scores  $<-2.0$ , and minimal or no exposure to bisphosphonates. The women treated with denosumab had significantly greater increases in BMD at all sites when compared with alendronate, and greater suppression of bone remodeling markers [51].

The STAND study (Study of Transitioning from Alendronate to Denosumab) compared the efficacy and safety of patients transitioning from alendronate to denosumab during a 1-year period versus patients who continued with alendronate. The study was a multicenter, randomized, double-blind study that included 504 postmenopausal women with T-scores  $\leq -2.0$  who had been receiving alendronate for at least 6 months. The study showed that the transition from alendronate to denosumab is safe and results in greater increases in BMD in the lumbar spine, femoral neck, and distal radius when compared to the continued use of alendronate ( $p \leq 0.0125$ ). The administration of denosumab further reduced levels of sCTX and PINP when compared to continued use of alendronate [52].

In the DECIDE and STAND studies combined, approximately 65 % of the patients expressed a preference for biannual injections as opposed to daily oral administration [53].

More recently, an extension study evaluated the effects of continued treatment with denosumab over an 8-year period, showing a constant reduction in bone turnover markers, and continuous increases in BMD, achieving a total gain of 16.5 % in the lumbar spine and of 6.8 % in the hip [49].

## Parathyroid Hormone

Despite the well-known deleterious effect of parathyroid hormone (PTH) on bone, the intermittent administration of recombinant human PTH (1–84 or 1–34) is known to stimulate bone formation rather than resorption, and is effective in reducing fractures in women with postmenopausal osteoporosis.

PTH 1–34 (Teriparatide, Forteo®) and PTH 1–84 (PreOs) belong to a new class of medications, known as anabolic agents. Teriparatide is available in the USA and Europe for the treatment of severe osteoporosis, and PTH 1–84 has been approved in Europe.

Most of the gain in BMD with the use of PTH occurs within the first few months, although anti-fracture efficacy is evident only after 6 months of treatment. BMD is markedly increased (more than treatment with anti-resorptive agents) at locations predominantly formed of trabecular bone, such as vertebrae. When the bones are predominantly cortical, such as radius bones, there is no gain. Furthermore, there is evidence that seems to indicate that alterations in BMD from the use of PTH start to diminish after 18 months [54].

So far, teriparatide has proved to be safe and effective for up to 2 years of treatment. The recommended dose is 20 mg daily SC, with no need for dose adjustment due to renal or hepatic impairment, since the drug is rapidly absorbed and eliminated.

The Fracture Prevention Trial (FPT) studied the use of teriparatide (20 mcg or 40 mcg/daily) in 1,637 postmenopausal women with prior vertebral fractures, compared with a placebo group [54]. After 18 months of treatment, it was observed that in the group receiving 20 mcg, BMD increased by 9 % at the lumbar spine, and by 3 % in the femoral neck. In the group receiving 40 mcg, BMD increased by 13 % at the lumbar spine and 6 % in the femoral neck. There was also a significant reduction in the risk of vertebral and non-vertebral fractures when compared to the placebo group, but not in a dose-dependent manner. It was not possible to obtain complete data on hip fractures, since the number of cases was very small.

An extension of the FPT evaluated participants for another 18 months after discontinuation of teriparatide [55], and found that women who used teriparatide showed a small decrease in BMD, but that a reduction in vertebral fracture risk persisted (relative risk reduction of 40 % when compared to the placebo group).

Similarly, teriparatide and PTH 1–84 showed higher increases in bone remodeling markers between the first and third month of treatment, especially the bone formation markers (sNTx and P1NP). This peak of remodeling markers is associated with greater increases in BMD [56].

The PaTh study evaluated the combination of alendronate with teriparatide in order to determine whether the combination of drugs would decrease the anabolic effect of PTH. The BMD of the lumbar spine, as well as that of the femoral neck, presented greater increases in the group receiving teriparatide alone than in groups that received alendronate alone, or in combination, demonstrating that alendronate reduces the ability of teriparatide to increase BMD [57].

The effects of combination therapy using zoledronic acid with teriparatide in women with postmenopausal osteoporosis were evaluated over a 1-year period, showing a greater and more rapid increase in lumbar spine and hip BMD than when either of the two drugs was administered alone [58].

Concern exists regarding the potential loss of bone mass that may occur after discontinuation of treatment with PTH. Nonetheless, several studies have shown that treatment with bisphosphonate, estrogen, or raloxifene after discontinuation of PTH preserves the bone mass gain achieved by PTH [59–61].

Parathyroid hormone therapy is indicated in more severe cases of osteoporosis (especially with multiple fractures), very low T-scores ( $< -3.0$ ) even without fractures in very elderly patients, those with bisphosphonate intolerance, and/or when dealing with fractures potentially affected by anti-resorptive agents.

The main adverse effects of PTH use are nausea, headache, and hypercalcemia and are of more frequent occurrence at higher dose levels. The use of PTH is contraindicated in children and young adults with epiphyses that are still open, tumors or

bone metastases, and hypercalcemia. Although the risk is only theoretical, and demonstrated only in mice, patients at high risk for osteosarcoma should also avoid using this medication.

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## Strontium

Strontium ranelate consists of two stable strontium atoms attached to an organic compound, ranelic acid. The exact mechanism of strontium action in humans remains unknown, with some possible mechanisms having been proposed. These include regulation of bone cell differentiation, stimulation of osteoblast proliferation, inhibition of osteoclast formation, activation of calcium-receptor sensors, increased expression of OPG, and the stimulated proliferation of preosteoblasts [62, 63]. Its use has been approved in Europe, but not in the USA.

In patients taking strontium, the assessment of BMD is not a good indicator of fracture risk reduction, because the medication is incorporated into the bone, thereby weakening DXA ray penetration, since it has an atomic number greater than that of calcium, and can cause overestimation of the BMD [63].

Several clinical studies have confirmed the effectiveness of strontium ranelate use for the treatment of postmenopausal osteoporosis. The SOTI (Spinal Osteoporosis Therapeutic Intervention) study [64] evaluated women with previous vertebral fractures, and the use of strontium was associated with a 49 % reduced risk of vertebral fractures in the first year, and a 41 % reduction in risk after 3 years, while the TROPOS (Treatment of Peripheral Osteoporosis ) study [65] demonstrated a 16 % reduction in the relative risk of all non-vertebral fractures over 3 years. During the studies, increases in markers for bone formation and reductions in markers for resorption were observed, data consistent with the idea that this medicine works by stimulating bone formation and inhibiting bone resorption [64, 65].

A meta-analysis of four studies (including those mentioned above) concluded that evidence exists that strontium ranelate is effective in reduc-

ing the risk of vertebral fractures, and to a lesser extent, non-vertebral ones [66].

The main side effects associated with use of the medication are nausea and diarrhea, which occur most frequently during the first 3 months of treatment. Serious adverse effects such as severe skin reactions (Stevens-Johns, toxic epidermal necrolysis, DRESS—Drug Reaction With Eosinophilia and Systemic Symptoms), in addition to venous thromboembolism have been reported. However, an extension study lasting 10 years showed that long-term treatment with strontium is associated with sustained increases in BMD, and that it has a good safety profile, showing no cutaneous hyper-sensibility reactions, and that the annual incidence of venous thromboembolism was only 0.4 % [67]. In any case, the medication is not recommended for patients with previous episodes of venous thromboembolism or those who are immobilized, and should be discontinued in the case of skin reactions with no resumption of treatment.

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## Future Perspectives

### Cathepsin K Inhibitors (Odanacatib)

Cathepsin K is a protease, found in osteoclasts, which degrades type I collagen, playing a role in bone resorption mediated by osteoclasts. Cathepsin K inhibitors (such as Odanacatib) decrease bone reabsorption and have improved BMD in vitro and in vivo.

A 2-year placebo-controlled study of postmenopausal women with low bone mass showed increased BMD of the lumbar spine (5.5 %) and hip (3.2 %) in the group treated with 50 mg of odanacatib per week, with good levels of safety and tolerability [68].

Extension of the study for 1 more year (for total of 3 years) demonstrated that the group that continued treatment showed a progressive increase in BMD in the spine and hip, and constant suppression of NTx. The group that discontinued treatment showed bone loss at all sites, but maintained a BMD greater than, or equal to, the baseline [69].



## Anti-sclerostin

Sclerostin is produced by osteocytes, and has an inhibitory effect on bone formation. In animal trials, the administration of a monoclonal anti-sclerostin antibody has resulted in increased bone mass [70, 71].

In a phase I study, 72 healthy subjects were randomly selected to receive either AMG 785 (an anti-sclerostin monoclonal antibody) or a placebo subcutaneously or intravenously administered in a single dose. AMG 785 was well tolerated, and dose-dependent increases in markers for bone formation, decreased resorption markers, and significant increases in BMD at the lumbar spine (5.3 %) and hip (2.8 %) were all observed when compared to the placebo group. However, further clinical research is still needed on sclerostin inhibition as a potential therapeutic strategy for the treatment of osteoporosis [72].

## Transdermal PTH

The transdermal administration of PTH is made via an adhesive patch with 1,300 micro-needles coated with teriparatide, and is an alternative to treatment with PTH SC. It is a well-tolerated medication, with its most common adverse side effect being transient erythema at the application site.

The effectiveness of this patch was evaluated in a phase II clinical trial with 167 randomly chosen women with postmenopausal osteoporosis divided into three groups receiving: transdermal teriparatide (20, 30 or 40 mcg/day); an adhesive placebo; or SC injection of teriparatide (20 mcg/day) [73]. After 6 months, the BMD in the group that received transdermal PTH was significantly higher than in the placebo group, and similar to that of the SC PTH group. With the transdermal application, a rapid increase was shown in the plasma concentration of teriparatide, followed by a rapid fall, a pattern that is required for an anabolic effect. In addition, the patch resulted in a higher peak, and a shorter plasmatic half-life of teriparatide than with SC injection, a finding that may signal a greater anabolic effect.

## Oral Calcitonin

An additional treatment option for women with postmenopausal osteoporosis is oral recombinant salmon calcitonin (rsCT). Its efficacy and safety were assessed in a phase 3 study, which showed that oral treatment resulted in an increase from baseline in the lumbar spine BMD greater than that with nasal spray calcitonin or placebo (1.5 % ± 3.2 % versus 0.78 % ± 2.9 % and 0.5 % ± 3.2 %, respectively). Oral rsCT treatment also resulted in greater improvements in trochanteric and total proximal femur BMD and better reductions in bone resorption markers. Oral rsCT was safe and well tolerated. The main adverse events were in the gastrointestinal system; less than 10 % of women experienced a serious adverse event and no deaths occurred in this study [74].

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### Clinical Case

A 71-year-old male was referred for a diagnostic evaluation of osteoporosis. Although the patient had no complaints, his primary care physician obtained a screening bone density test, in view of his age. There is a strong family history of osteoporosis on his paternal side with his father, aunts, and uncles all affected. He has never had a fracture. He has never had a kidney stone. The patient drinks one glass of wine on average per night, and smokes cigarettes (30 pack-years). There is no history of corticosteroid, thyroid hormone, or antiseizure medication use. His diet is relatively poor in calcium-containing foods but, recently, he has added a calcium supplement with vitamin D to his regimen. His exercise routine, over the past 10 years, consists of swimming and walking three times per week. Recently, he has added weight-bearing exercises to his regimen. There has been no height loss from his peak of 180 cm.

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*Past medical history:* Hypertension, since age 65, is well controlled on angiotensin-converting enzyme therapy.

*Personal and social history:* Patient is married and has one daughter (50 years old) and one son (45 years old), both of whom are healthy.

*Family history:* Father died at 92 from an upper respiratory infection. His mother is 95 years old with hypertension and diabetes. He has no siblings. A strong family history for osteoporosis is as noted.

*Physical examination:* Height, 180 cm; weight, 104 kg; BMI, 32 kg/m<sup>2</sup>. There was no dorsal or supraclavicular fat pads. Examination of heart, lungs and abdomen was normal. There were no striae. The back was straight, without scoliosis or kyphosis. No physical findings of hypogonadism were detected.

*Laboratory results:* Calcium, 9.2 mg/dL (nl: 8.9–10.1); phosphorus, 3.4 mg/dL (nl: 2.5–4.5); PTH, 25 pg/mL (nl: 15–65); 25-hydroxyvitamin D, 35 ng/mL (nl: 30–50 ng/mL); alkaline phosphatase activity, 52 IU/L (nl: 33–96); and creatinine, 0.85 mg/dL (nl: 0.76–1.27 mg/dL). The estimated glomerular filtration rate was normal (89 mL/min/1.73 m<sup>2</sup>). Total testosterone was 528 ng/dL (nl: 260–1,000 ng/dL) with normal FSH and LH levels. Serologies for gluten enter-

opathy were negative. Liver function was normal. Serum and urine protein electrophoresis were normal. 24-h urine collection for calcium (180 mg/g creatinine) and cortisol (20 µg) was normal.

*Bone density results:* T-scores at the following sites were as follows: −3.0 (lumbar spine); −2.6 (total hip); −2.5 (femoral neck).

*Summary:* The patient has several risk factors for osteoporosis, namely, age, family history, and tobacco use. By densitometric criteria with T-scores < −2.5, he has osteoporosis and is a candidate for therapy with pharmacological agents.

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## Key Points to the Diagnosis of Bone Loss in Men

The information to be presented in this discussion is based upon general and specific review material as described in the abstract [1–12].

## Medical History and Physical Examination

A complete review of systems draws attention to potential causes of bone loss by eliciting symptoms such as weight loss, change in body shape, bruising, hair pattern, libido, alcohol intake, smoking, and kidney stones. A medication history focuses upon thyroid hormone, glucocorticoids, and antiepileptic medications. The physical examination should always include height so that a comparison can be made with the historical record of peak height. Height loss of more than 5 cm calls for imaging studies [X-ray or vertebral fracture assessment by dual energy X-ray absorptiometry (DXA)] to investigate the possibility of a vertebral fracture. The presence or absence of kyphosis and/or scoliosis should be noted. Mobility and overall frailty are observed. Signs of common secondary causes of osteoporosis are sought: hypogonadism (testicular size, hair pattern), hyperthyroidism (neck exam, reflexes),

Cushing's syndrome (supraclavicular fat pads, skin thickness, striae, proximal muscle weakness), chronic obstructive pulmonary disease (anterior-posterior chest diameter, distant breath sounds), alcoholism (liver size, palmar erythema). Any of these findings can be helpful clues to the differential diagnosis of osteoporosis.

## Laboratory Tests

Laboratory tests should include serum calcium, phosphate, albumin, creatinine with estimated glomerular filtration rate, alkaline phosphatase activity, liver and thyroid function tests, 25-hydroxyvitamin D, parathyroid hormone, total testosterone, complete blood count and 24-h urine for calcium excretion. Depending upon the history and the physical examination, additional laboratory tests should be considered (i.e., cortisol, gluten antibodies, tryptase [13]).

## Bone Mineral Density (BMD)

The gold standard for the diagnosis of osteoporosis in men and women is the BMD measurement by DXA. Recent guidelines of The Endocrine Society [14] recommend that all men over 70 years old should have a screening BMD test, in agreement with previous recommendations by the International Society of Clinical Densitometry and the National Osteoporosis Foundation in the USA [15]. BMD should also be obtained in men under the age of 70 who have other risk factors for osteoporosis such as excessive alcohol intake, smoking, rheumatoid arthritis, glucocorticoid use (>5 mg prednisone or equivalent for >3 months), use of gonadotropin-releasing hormone agonists, low body weight, chronic obstructive pulmonary disease, hyperparathyroidism, hyperthyroidism, hypogonadism, delayed puberty, or family history of hip fracture [16–19]. Some experts advocate extending this screening window to men with hypercalciuria/nephrolithiasis, and those with a history of constitutionally delayed puberty.

A history of a fragility fracture after the age of 50 is another indication for a BMD test.

Vertebral or hip fractures occurring under these circumstances are particularly noteworthy.

A history of a fragility fracture, defined as a fracture occurring spontaneously or after minor trauma (i.e., a fall from a standing height), can be diagnostic of osteoporosis. In this case, a BMD test is performed not to make the diagnosis of osteoporosis but rather to determine the extent of bone loss and its pervasiveness.

BMD of spine and hip are the usual DXA measurement sites. If one of these regions cannot be interpreted (e.g., osteoarthritic changes in the lumbar spine), the forearm at the distal 1/3 radius is recommended. Forearm DXA is also recommended in those with primary hyperparathyroidism, hyperthyroidism, and those on androgen deprivation therapy (ADT) [14]. The diagnosis of osteoporosis is established with a BMD T-score of  $-2.5$  or less (i.e., 2.5 standard deviations below average peak BMD) [20]. There is controversy as to which reference range should be used to calculate T-scores in the male population. The Endocrine Society Guidelines and the International Society of Clinical Densitometry [14, 21] both recommend the male-specific reference range (peak bone mass for 25–30 year-old young men who have achieved peak bone mass) although other groups recommend the female database [22]. The uncertainty over which referent database to use is a result of a differing opinion as to whether absolute fracture risk or relative fracture risk should be used. The argument for using a male referent database for men is that the relationship between BMD and fracture risk is similar among men and women. For every SD unit reduction in BMD by DXA, fracture risk is doubled in men and in women. Therefore, the relative risk using the male referent database is the same for a T-score of  $-2.5$  as it is for a woman whose T-score is  $-2.5$  using a female referent database. Even though relative risk is the same, using the gender-specific referent standard, absolute risk is not. A man's T-score of  $-2.5$  confers a lower absolute risk of fracture than a woman's because the risk of fracture is lower in men than in women at any T-score. This latter point has led experts to recommend that the female database be used for both men and women. The absolute

risk of fracture is a function of the absolute BMD in  $\text{g}/\text{cm}^2$ , not the T-score. If this approach is taken, however, the diagnosis of osteoporosis in men will be made much less frequently and will be inconsistent with epidemiological data on fracture incidence in men. Therefore, utilization of the male database seems to make more sense.

## FRAX®

The fracture risk calculation tool FRAX®, approved by the World Health Organization in 2008 (<http://www.shef.ac.uk/FRAX/index.jsp>), is widely used in many countries throughout the world, including Brazil and other Latin American countries. FRAX® helps to identify those with osteopenia who are at high risk for fracture. FRAX® incorporates established clinical risk factors besides BMD (e.g., height, weight, age, sex, family history of hip fracture, glucocorticoid use, rheumatoid arthritis, alcohol intake, smoking, secondary causes of osteoporosis) and calculates a 10-year probability of hip fracture and major osteoporotic fracture (clinical vertebral, hip, forearm, or humerus). FRAX® is a country-specific algorithm, applicable to men and women [23, 24], with each country setting its threshold for therapeutic intervention according to its own cost effectiveness measures. In the USA, treatment with a pharmacological agent is recommended if the 10-year fracture risk by FRAX® for a major osteoporotic fracture is  $\geq 20\%$  or for hip fracture is  $\geq 3\%$ .

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## Differential Diagnosis of Bone Loss in Men

About 40–50 % of men diagnosed with osteoporosis will be shown, upon further evaluation, to have a secondary cause of bone loss [25]. Excessive alcohol intake, hypogonadism, and glucocorticoid excess are the three most important causes of secondary osteoporosis in men [26]. Other important etiologies to be considered are gastrointestinal disorders (e.g., celiac disease can be subclinical), hypercalciuria, chronic

obstructive pulmonary disease, organ transplantation, neuromuscular disorders, systemic illnesses (i.e., multiple myeloma), and medications [27]. In the setting of a fragility fracture, it is necessary to rule out the possibility of a pathologic fracture due, for instance, to a skeletal metastasis (i.e., prostate, lung).

It is not uncommon for there to be no obvious etiology to the osteoporosis, besides aging itself. In men over the age of 70, it is appropriate to use the term age-related osteoporosis. In individuals who are younger, however, aging is an incomplete explanation, particularly in view of the fact that age-related bone loss in men typically does not begin until around the age of 60. For want of a better word, the term used for these individuals is “idiopathic” osteoporosis, and, as noted, is applied often to osteoporotic men in their middle years. The term “idiopathic” does not mean to imply that there is no cause, but merely that a cause is not apparent. Studies of idiopathic osteoporosis have focused upon genetic predispositions [28], polymorphisms of the aromatase gene [29, 30], and deficiencies in the insulin-like growth factor system. Patients with insulin-like growth factor deficiency present with a low bone turnover state, with paucity of osteoblasts and osteoclasts on the bone surface and osteoblast dysfunction with decreased osteocalcin production, associated with low insulin-like growth factor levels [31–33].

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### Treatment: New and Future Therapies

The Endocrine Society recommends pharmacologic therapy for men who are at high risk for fracture. The indications in men are as follows: the presence of a fragility fracture (clinical or morphometric vertebral or hip); T-score at the lumbar spine, femoral neck, and/or total hip that is  $\leq -2.5$ ; in the US for those who have a T-score between  $-1.0$  and  $-2.5$  but in whom FRAX calculates a risk for any type of fragility fracture in the next 10 years  $\geq 20\%$ , and for hip fracture is  $\geq 3\%$ ; and long term glucocorticoid therapy [14].

Most of the pharmacologic agents that are currently available for men with osteoporosis have been previously tested and approved for women. The studies in men, in general, have not had adequate numbers of patients to ascertain a change in fracture incidence. Rather, other surrogate endpoints such as increases in BMD and changes in bone turnover markers have been used. On the whole, however, even without hard fracture endpoints, it seems that the efficacy of these drugs in men is similar to that in women [14]. Medications available at this time to treat male osteoporosis can be grouped according to their chemical class and function.

### Bisphosphonates

The current bisphosphonates approved by the FDA for the treatment of male osteoporosis are alendronate, risedronate, and zoledronic acid [34–42]. These bisphosphonates have been shown to increase BMD and to reduce bone turnover markers in men with osteoporosis. Alendronate and risedronate are oral bisphosphonates, requiring patients to take the drug in the morning, on an empty stomach with plain water and to wait approximately 30 min before eating, drinking, or taking other medications [43]. A new formulation of risedronate (DR 35 mg) can be taken before or after breakfast [44].

*Alendronate* is given weekly (70 mg) although the daily 10 mg formulation is still available. Both the weekly and the daily formulations increase BMD in men and reduce bone turnover markers. Men with osteoporosis treated for 2 years with daily alendronate 10 mg had a lower fracture incidence and less height reduction compared to those in the placebo group, with BMD increments at the lumbar spine (+7.1%), femoral neck (+2.5%), and total body (+2.0%) compared to baseline values [45]. Similarly, another study showed that treatment with alendronate 10 mg daily for 3 years promotes BMD gains at the lumbar spine (+8.8%), femoral neck (+4.2%), and total hip (+3.9%) [40]. Daily and weekly alendronate was associated with the same increments



in BMD [46]. A meta-analysis has provided additional support for the effects of alendronate to reduce vertebral fracture incidence in men [47].

*Risedronate* is effective in the treatment of primary and secondary causes of bone loss in men [38, 48]. Risedronate is taken either daily (5 mg), weekly (35 mg), or monthly (150 mg), the latter two being the most commonly used regimens. In an open label clinical trial conducted by Ringe et al., daily treatment with risedronate 5 mg for 1 year reduced the incidence of a new vertebral fracture by 60 % compared to placebo which was sustained for the second year of treatment and associated with BMD improvements at the lumbar spine (+6.5 %); femoral neck (+3.2 %), and total hip (+4.4 %) [38, 48]. In a 2-year, randomized, double-blind, placebo-controlled study in men with osteoporosis, Boonen et al. demonstrated that weekly risedronate is as effective as daily risedronate in terms of reductions in bone turnover markers and increases in BMD [49]. There were very few fractures in that study and a difference between placebo and the treatment arms could not be ascertained. In a 2-year open-label extension of this trial, risedronate was associated with further increases in BMD [50]. Risedronate has also been shown to be effective in the treatment of bone loss in men >65 years of age who have sustained a cerebrovascular accident. Although the number of hip fractures was small (10 in the placebo vs. 2 in the risedronate groups), risedronate was associated with a significant reduction in hip fracture incidence [51].

*Zoledronic acid* is administered intravenously at a dose of 5 mg once yearly for the treatment of osteoporosis. Satisfactory results with this drug were observed in osteoporotic men [39]. Zoledronic acid is as effective as alendronate in increasing BMD and reducing bone turnover markers the men with idiopathic osteoporosis or osteoporosis due to hypogonadism [52]. Moreover, in the treatment and prevention of glucocorticoid-induced osteoporosis, zoledronic acid was superior to risedronate in increasing BMD and reducing bone turnover markers [53]. A double-blind, randomized placebo-controlled registration trial for zoledronic acid, known as The Health Outcomes and Reduced Incidence with

Zoledronic Acid Once-Yearly Recurrent Fracture Trial (HORIZON-FT), enrolled men and women with a recent low-trauma hip fracture (within 90 days of surgical repair). Boonen et al. conducted a subset analysis grouping the results by gender [54]. Patients were randomized either to yearly infusion with zoledronic acid or placebo for 24 months, with a mean follow-up of 21 months. In the group treated with zoledronic acid, adjusted BMD increased significantly at the total hip (+3.8 %) and femoral neck (+3.1 %) as compared to the placebo group ( $p < 0.01$  for all comparisons). Increments in BMD in men were similar to the increments in the women, demonstrating clearly that zoledronic acid increases BMD in men with history of a recent hip fracture [54].

Most of the aforementioned studies of bisphosphonates in men have focused upon equivalency data with regard to BMD and bone turnover markers in the intention-to-treat analyses. While these studies have provided some evidence for fracture reduction, there had not been a prospective, randomized, double-blinded, placebo-controlled trial of a bisphosphonate statistically powered to show a reduction in fracture incidence until recently. Boonen et al. conducted such a study in a major clinical 2-year, placebo-controlled trial of 1,199 men, 50–85 years old, with primary or hypogonadism-associated osteoporosis [55]. Zoledronic acid or placebo was administered at baseline and at 1 year. An important feature of this trial is that it was powered to determine a difference in fracture endpoints. The primary endpoint was the percentage of men who sustained 1 or more new morphometric vertebral fractures after 24 months. Overall, patients treated with zoledronic acid had a 67 % reduction in relative fracture risk and a 3.2 % risk reduction in absolute risk (4.9 % vs. 1.6 %;  $p = 0.0016$ ). Furthermore, the group that received active drug experienced fewer moderate to severe vertebral fractures ( $p = 0.026$ ) and less height loss ( $p = 0.0002$ ) in comparison to placebo. Men with osteoporosis due to hypogonadism demonstrated results similar to the group with normal testosterone levels. No difference was seen between serious adverse events in the zoledronic acid and placebo groups [55].

## Osteoanabolic Therapy

The two available osteoanabolic treatments for osteoporosis are PTH(1-84), the full length, native molecule, and its foreshortened analogue PTH(1-34), known as teriparatide. Teriparatide is approved worldwide including Europe, Brazil, and the USA for the treatment of men and postmenopausal women with osteoporosis at high risk for fracture and for the treatment of glucocorticoid-induced osteoporosis. PTH(1-84) is approved for the treatment of postmenopausal osteoporosis in a several number of countries, but not in the USA or in Brazil.

Teriparatide is administrated as a daily 20 µg subcutaneous injection for no more than 2 years. Orwoll et al. showed that treatment with teriparatide for 11 months in men with idiopathic osteoporosis or osteoporosis due to hypogonadism increases BMD to virtually the same extent as in women over that same period of time [56]. Participants were followed for 30 months after the drug was discontinued due to early termination of the trial. Over this period of time some received antiresorptive therapy. After discontinuation 18 months later, there was an overall reduction in moderate to severe vertebral fractures when the original teriparatide treatment groups (20 and 40 µg) were compared to the original placebo group [57]. In glucocorticoid-induced osteoporosis, a clinical trial in which men were included showed that teriparatide promotes better BMD outcome and lower vertebral fractures when compared with patients treated with alendronate [58, 59]. As shown in the study of Kaufman et al. [57] as well as other studies, discontinuation of teriparatide therapy is associated with rapid reductions in BMD if a bisphosphonate is not used promptly thereafter [60].

In women who have previously been treated with an antiresorptive drug and sequentially with teriparatide, the actions of teriparatide may be delayed [61]. However effects of prior bisphosphonate therapy are overcome, usually with the first 6 months of PTH treatment. In men, simultaneous therapy with teriparatide and alendronate gave no densitometric advantage over monotherapy with teriparatide alone [62]. Walker et al. have recently reported a randomized, double-blind

study to evaluate the combination of teriparatide and risedronate. A total of 29 men, aged 37–81, with low BMD at the spine, hip, or distal radius were enrolled [63]. Patients were randomized to receive risedronate 35 mg weekly plus daily-injected placebo, teriparatide 20 µg subcutaneously daily plus weekly oral placebo, or both risedronate plus teriparatide (combination) for 18 months. BMD gains at the lumbar spine were seen in all three groups ( $p < 0.05$ ), but there were no between-group differences. However, total hip BMD increased to a greater extent in the combination group ( $3.86 \pm 9.2\%$ ) versus teriparatide ( $0.29 \pm 8.0\%$ ) or risedronate ( $0.82 \pm 8.0\%$ ;  $p < 0.05$  for both). Femoral neck BMD also increased to a greater extent in the combination group ( $8.45 \pm 14.1\%$ ) versus risedronate ( $0.50 \pm 12.2\%$ ;  $p = 0.002$ ), but was not different from teriparatide alone.

The safety of teriparatide has recently been reviewed with specific reference to reports of osteosarcoma in rats when administered very large doses for a large proportion of a rat's life [64, 65]. The 10-year history of parathyroid hormone as a treatment for osteoporosis does not provide any evidence that osteosarcoma is a risk when teriparatide or PTH(1-84) is used for the treatment of osteoporosis [66, 67].

## Strontium Ranelate

Strontium ranelate is registered as a treatment for osteoporosis in many countries, including Brazil, but it is not available in the USA. Clinical trials in postmenopausal women have shown that strontium ranelate increases BMD and reduces the risk of vertebral fractures and to a lesser extent non vertebral fractures [68]. However, the mechanism by which strontium ranelate reduces fracture is still not fully understood [69]. In a study of 152 men with primary osteoporosis, subjects were randomized to receive alendronate 70 mg per week or strontium ranelate 2 g per day for 12 months. All patients received calcium and vitamin D supplementation. Both groups experienced increments in BMD at lumbar spine and at total hip at the end of the trial. However, patients treated with strontium ranelate experienced a greater increase than those who took alendronate (by 22 % at lumbar spine and 23 % at total hip) [70].

A major factor that helps to explain the major increase in BMD when strontium ranelate is used is the actual incorporation of the strontium element into the bone crystal. This may account for as much as 75 % of the increment in BMD.

## Testosterone

Treatment of male osteoporosis with testosterone focuses upon men with hypogonadism. There is no rationale for using testosterone in men who are eugonadal. In hypogonadal men, testosterone leads to an increase in bone mineral density and a reduction in bone turnover markers [71–73]. Evidence, however, for fracture efficacy is weak. Therefore, the recent recommendations of The Endocrine Society emphasize the use of bisphosphonates and other approved therapies for hypogonadal men [14]. Testosterone is recommended under certain conditions, however, such as in men at borderline high risk for fracture who have serum testosterone <200 ng/dL and one of the following: known hypothalamic–pituitary–gonadal disorders, symptoms of androgen deficiency or contraindications to other approved pharmacologic agents to treat osteoporosis. If hypogonadal symptoms are not ameliorated after 6 months of therapy, testosterone should be discontinued and another therapy should be considered. For hypogonadal men who are at high risk for fractures, a non-androgenic, approved drug is recommended with testosterone also if the patient is symptomatic of androgen deficiency and there are no contraindications [14].

## Selective Estrogen Receptor Modulators (SERMs)

The rationale for considering an estrogen-like treatment for osteoporosis in men rests with the studies clearly linking estrogen deficiency to age-related bone loss in men and the pivotal role that estrogen plays in the acquisition of peak bone mass in men. SERMs are attractive because at bone they act as estrogen agonists [74, 75]. In a small, cross-over study by Ueblehart et al., raloxifene was used to treat eugonadal osteoporotic

men [76]. Subjects received either daily oral raloxifene 120 mg or placebo for 2 months before crossing-over. On raloxifene, bone resorption markers were reduced if baseline estradiol levels were low. Toremifene, another SERM, was used in men receiving androgen deprivation therapy for prostate cancer [77]. After 2 years, toremifene was associated with increased BMD and a 50 % risk reduction of new vertebral fractures in comparison to placebo. Adverse events were similar to placebo with the exception of venous thromboembolic events (toremifene 2.6 % vs. placebo 1.1 %) [77]. The use of this class of agents for men is clearly in the early developmental stages and is not, therefore, generally recommended.

## Denosumab

Denosumab is a human IgG antibody that binds to and inactivates RANKL (receptor activator of nuclear factor- $\kappa$ B ligand) [78, 79]. This potent antiresorptive therapy was approved for postmenopausal women at high risk for fracture in the USA and Europe in June, 2010. It is administered subcutaneously at a dose of 60 mg every 6 months. Not cleared by renal mechanisms, it has been shown to be efficacious in subjects with creatinine clearance values <30 cc/min. Based on the study of Smith et al., in which denosumab was used to treat men undergoing ADT therapy, it received a specific indication for men on ADT [80]. Further clinical trials in men with osteoporosis demonstrated salutary effects on BMD along with a sustained suppression of bone resorption markers. Lumbar spine, total hip, and femoral neck BMD increased by 5.7 %, 2.4 % and 2.1 % respectively (adjusted  $p \leq 0.01$  for BMD percent differences at all sites compared with placebo) [81]. On the basis of this additional information, denosumab received an indication in the USA for men with osteoporosis at high risk for fracture in September, 2012.

## Future Therapeutic Approaches

### Cathepsin K Inhibitors

Cathepsin K, an osteoclast-derived protease, degrades type I collagen, the major component of the organic bone matrix. It plays an important

role, under normal circumstances, in initiating events that lead to the creation of the bone remodeling unit [82]. The development of cathepsin K inhibitors represents another step forward in establishing new classes of therapeutics for osteoporosis. Clinical trials of Odanacatib, a highly specific cathepsin K inhibitor, have shown that it potently reduces bone resorption to a much greater extent than bone formation. The rather small effect on bone formation markers as well as on bone formation dynamics by bone biopsy argues that this drug may not suppress bone formation to the same extent as other antiresorptive classes [82]. Clinical trials are promising [83–86]. In July, 2012, the data and safety monitoring board for the pivotal phase 3 clinical trial of Odanacatib recommended that the trial be stopped because therapeutic end points had been reached. So far, published studies are in women only, but clinical trials are being conducted in men [87].

### Sclerostin Antibody

Sclerostin, an osteocyte product, is regulated by the *SOST* gene. It plays a key role as a signaling molecule that mediates bone formation [88]. A sclerostin monoclonal antibody has been developed and is currently being tested. Although gender-specific results are not available yet, reports of a single-dose, placebo-controlled, randomized study of sclerostin monoclonal antibody, which enrolled both men and women, showed that bone formation markers increased markedly along with a substantial reduction in bone resorption markers [89].

### Nonpharmacologic Approach

Lifestyle modifications should be encouraged for all men with osteoporosis, including adequate calcium and vitamin D intake and regular exercise [16, 90]. The daily calcium intake for men should be 1,000–1,200 mg [91] and preferably from dietary sources. Supplemental calcium should be used if dietary sources are insufficient. Although the Institute of Medicine suggests that the target for 25-hydroxyvitamin D level is 20 ng/mL rather than 30 ng/mL [91], most authoritative

organizations have opted to maintain the recommendation of 30 ng/mL for men with osteoporosis [92, 93]. Smoking and alcohol are contributing risks for bone loss, and thus patients should be encouraged to stop smoking and to limit alcohol intake to 2 drinks per day.

### Monitoring Therapy

The International Society of Clinical Densitometry recommends that patients who are being treated with pharmacological agents should be monitored every 1–2 years with DXA [21]. If BMD stabilizes, the frequency of DXA monitoring can be reduced. Bone turnover markers should be considered as a surrogate tool to assess the status of bone formation and bone resorption, and can be useful as early as 3–6 months after initiation of treatment.

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## Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a hereditary disorder of the connective tissue. It is caused by qualitative or quantitative abnormalities involving type I collagen, with varied phenotypic presentations. Patients who are affected may suffer multiple fractures, at times with little or no trauma. In more serious cases, death may occur during the neonatal period. Mild and moderate forms can manifest as premature osteoporosis or severe mineral loss in the bones during postmenopause. Some patients also exhibit blue sclera. The incidence of OI is approximately 1 in every 20,000–25,000 live births in the USA [1].

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## Pathophysiology

Type I collagen is a structural protein important to bones, tendons, ligaments, skin, and sclera. OI is commonly caused by mutations in genes forming the code in the alpha-1 and alpha 2 chains within type I collagen, or proteins involved in the formation of type I collagen. The fibrils of type I collagen are composed of polymers of tropocollagen molecules that form a triple helix containing portions of an alpha-1 chain, and two alpha-2 chains [2, 3].

Most patients with OI exhibit a dominant autosomal mutation in COL1A1 (located at 17q21.31-q22) or COL1A2 (located at 7q22.1) that affects the structure of one of the two alpha chains of type I collagen. The clinical severity depends on the effect of the mutation. Mutations that lead to reduction in the amount of collagen result in less severe phenotypes (OI type I), in contrast to mutations that disrupt the formation of triple-helix collagen that lead to lethal forms (type 2 OI). Ten percent of patients have a recessive autosomal genetic defect, as with normal COL1A1 and COL1A2 genes.

Mutations in the gene of the FK506-binding protein (FKBP10 or FKBP65), located at 17q21, were identified in samples from five consanguineous families from Turkey and Mexican families with hereditary characteristics causing moderate-to-severe OI [4]. Mutations in the FKBP10 protein, which affect the secretion of type I pro-collagen, in addition to causing type III OI, may result in a severe form of isolated type IV OI that begins during the prenatal stage [5].



**Table 26.1** Osteogenesis imperfecta symptoms

Osteogenesis imperfecta symptoms		
Atypical fractures	Short stature	Scoliosis
Blue sclera	Hearing loss	Dentinogenesis imperfecta
Laxity of the ligaments	Wormian bones	Laxity of the skin

The recessive form of osteogenesis is caused by a deficiency or a mutation in one of the three components of the 3-prolyl hydroxylation complex that modifies the structure of type I collagen, and can cause severe to lethal forms of the disease [6]. Mutations causing severe recessive forms can be identified in other genes that encode proteins involved in bone formation and homeostasis, including *SERPINH1* (located in t 11q13.5), *SERPINF1* (located in 17p13.3), and *SP7/OSX* (located in 12q13.13) [7, 8]. The presence of abnormal protein structure determines bone fragility.

Disorganized bone structure can be observed histologically, in many cases with normal mineralization, but with significant reduction in cortical thickness, cancellous bone volume, and the number and thickness of trabeculae. A cross-sectional study compared the microstructure and bone density in 39 patients with type I OI with 39 controls. Twenty-seven patients had been treated with bisphosphonates. High-resolution computerized tomography was performed on the distal radius and tibia, as well as bone densitometry (BMD) of the lumbar spine and femoral neck. Patients with OI were shorter in stature, but with similar body weight. BMD values were lower for the hip and lumbar spine in OI patients when compared with control patients. The bone area in the radius was 5 % lower in patients with OI, and 18 % lower in the cortical bone, and the trabecular number was significantly lower in patients than in controls [9].

## Clinical Manifestations

The clinical features (Table 26.1) range from intrauterine fractures to fractures that normally occur only in adolescence and adult life. Fractures

are the result of minimal trauma and bone deformities may occur. Family members with the same mutation may exhibit differing degrees of severity, most likely resulting from defects affecting other components of the connective tissue.

The types of OI can be divided according to their severity (Table 26.2):

- Mild (type I): Patients with type I OI suffer from few or no fractures before puberty, or sometimes numerous fractures throughout their lives. The deformities are minimal, and the individuals usually have lower than normal stature. Frequently, no fractures occur before the child begins to walk. The long bones of the arms, legs, and ribs are most often affected, as well as the small bones of the hands and feet. The frequency of fractures decreases after puberty. In adults there is premature osteoporosis and early hearing loss.
- Moderate to severe (type III–IX): These children have a high frequency of fractures, moderate-to-severe bone deformities, kyphoscoliosis, short stature, and progressive hearing loss, with some children unable to move around. Adults exhibit early osteoporosis and hearing loss, more severe when compared with the mild form. Pregnant women exhibit accelerated bone loss during pregnancy and breastfeeding. Hypermobility of the joints can lead to pain and diminished function.
- Lethal form (type II): Patients with the lethal perinatal form usually have intrauterine death, or die during early childhood. Fractures and respiratory insufficiency are frequent causes of death. In such cases, genetic counseling should be provided for families affected.

## Diagnosis

A diagnosis of OI should be considered in any child with recurrent fractures from minimal trauma [3]. Family history, clinical examination, and radiological findings are important for diagnostic confirmation. The clinical picture is not always characteristic. Extra-skeletal manifestations may be subclinical (hearing loss), nonspecific, or more common at some ages

**Table 26.2** Clinical characteristics according to the type of OI

Types of OI	Severity of fractures	Stature	Sclera	Hearing loss	Dentinogenesis imperfecta
I	Slight (<100)	Normal–slightly lower	Blue	Present in 50 %	Rarely
II	Perinatal death—multiple	Severely low stature	Blue	–	Yes
III	Severe—multiple	Very low	Blue at birth	Frequent	Yes
IV	Mild to moderate	Variable	Normal	Sometimes	Sometimes
V	Moderate—multiple	Variable	Normal	No	No
VI	Moderate	Slightly lower	Normal—discretely blue	No	No
VII	Moderate	Slightly lower	Normal—discretely blue	No	No
VIII	Severe/lethal	Short members dwarfism	Normal	Not related	No
IX	Severe/lethal	Short limbs	Blue	No	Yes

(dentinogenesis imperfecta is most notable in the first dentition).

- Imaging studies: X-rays of long bones and the spine may show fractures, bone calluses, or deformities, and the X-rays of the skull may reveal the presence of wormian bones.
- Laboratory: Assessment of calcium metabolism (serum calcium, phosphorus, alkaline phosphatase, and PTH) is useful to rule out any preexisting hypocalcaemia or hyperparathyroidism. In cases involving OI, the parameters are usually normal. In type VI OI, increases in alkaline phosphatase may occur. Hypercalciuria is common in children with OI, and the magnitude of the urinary calcium loss reflects the severity of bone disease (shorter height, and higher rate of fracture). Bone formation markers are usually low and markers for bone resorption (CTX) usually high, especially in the more severely affected patient [10, 11].

## Differential Diagnosis

Child victims of trauma, as well as patients with severe OI, may exhibit multiple fractures at different stages of fusion. In a study involving 39 children (older than 1 year of age) with fractured collarbones, 82 % were considered to be the result of child abuse, 8 % accidental injury, and 8 % bone fragility, and in one case fractures were the result of osteogenesis imperfect itself [12].

Another study evaluated 61 children victims of child abuse. After reviewing the medical records, 33 cases were confirmed as OI. The median age at

examination was 7.1 months. All patients had fractures, 14 exhibited pain, 7 swelling, 5 showed limited movements, and 2 showed an abnormal position of their limbs. Radiographic findings consistent with OI were found in 19 of 33 patients (58 %); clinical findings were present in 23 of 33 patients (70 %), and a family history of OI in 55 % [13]. Therefore, in cases where child abuse is suspected, OI should always be considered, since any error in diagnosis can lead to serious consequences for the children and their families.

The clinical picture of OI is not always characteristic. Patients with mild OI exhibit no fractures until they start to move around. Retinal hemorrhage, subdural hematoma, and bruising may also occur as indirect signs of trauma.

Rickets may cause slow growth, bone deformities, elevated alkaline phosphatase, defects in bone mineralization, and, in some cases, abnormal formation of the teeth. Abnormalities in the sclera and hearing loss typically do not occur and on X-rays, epiphyseal plate enlargement is present. In the adult patient, osteomalacia may cause bone pain, fractures, and elevated alkaline phosphatase, also without causing hearing loss or blue sclera. Radiological findings include decreased bone density, pseudofractures, and loss of trabecular definition.

Other rare skeletal syndromes causing bone fragility and deformities should also be considered in the differential diagnosis of OI and these include Bruck syndrome, osteoporosis pseudoglioma syndrome, polyostotic fibrous dysplasia, and juvenile Paget's disease, hypophosphatasia, and idiopathic juvenile osteoporosis.

**Table 26.3** Administration of pamidronate in children with OI

Age	Dose of pamidronate	Frequency
<2 years	0.5 mg/kg/day for 3 days	2/2 months
Between 2 and 3 years	0.75 mg/kg/day for 3 days	3/3 months
>3 years	1.0 mg/kg/day for 3 days	4/4 months

## Treatment

The focus of treatment should be multidisciplinary in order to oversee early care and minimize complications. The objective is to reduce the rate of fractures, prevent deformities, decrease chronic pain, and improve functional capacity.

Bisphosphonates are the main therapeutic agents used to prevent fractures in most forms (except for type VI) although none have been approved specifically for use in children and adults with OI. Bisphosphonates are stable pyrophosphate analogues, and are potent inhibitors of bone reabsorption and bone turnover.

The majority of studies was conducted in children and did not include control groups. Observed benefits included an increase in bone mineral density, reduced fracture rate, and improvement in mobility and pain [14]. Pamidronate is administered intravenously during consecutive 3-day cycles, with 2–4-month intervals, using 0.5 mg/kg/day up to 1 mg/kg/day depending on the age (Table 26.3).

Short-term adverse effects on bone quality and fracture healing are not present, despite the significant reduction in bone turnover with bisphosphonate treatment [15]. Linear growth does not appear to be affected and the greatest benefit seems to occur within the first 2–4 years of therapy. It is prudent to reserve pamidronate for patients in whom the clinical benefits outweigh the risks (deformity of long bones, vertebral compression fractures, and three or more fractures per year) since the long-term effects as yet are not well understood [16].

In a meta-analysis, oral risedronate (35 mg per week) for 24 weeks led to bone mineral density increases by 3.9 % at the lumbar spine without statistical significance in the total hip measurements.

Bone pain did not improve significantly, and the fracture rate remained high [17].

In most cases, orthopedic care focuses on fractures, but also should be considered for the correction and prevention of deformities, especially in the lower limbs, including surgical treatment.

## Osteomalacia

Osteomalacia is not a common metabolic bone disease, but is often neglected especially in its early stages because of the nonspecific nature of symptoms such as vague bone pain and muscle weakness [18]. The disease is characterized by a generalized weakening of bone, leading to deformity, and it is often caused by defects occurring at any step of the metabolism or action of vitamin D [19]. It occurs mostly due to dietary deficiency and exposure to sunlight, but can also be due to intestinal malabsorption, chronic kidney failure, or vitamin D resistance [18] (Table 26.4). Osteomalacia can also occur in patients with primary hypophosphatasia (Table 26.5) due to one of the syndromes of hereditary hypophosphatemia (X-linked, autosomal dominant and with hypercalciuria) or oncogenic due to fibroblastic growth factor-23 (FGF-23) secretion by the tumor [20, 21].

**Table 26.4** Etiology of osteomalacia

Causes of osteomalacia
Vitamin D deficiency
Lack of sunlight
Malabsorption syndrome
Liver diseases
Chronic renal insufficiency
Anticonvulsants
Reduced calcium intake
Heavy metals: Aluminum, lead, cadmium

**Table 26.5** Etiology of hypophosphatemic osteomalacia

Causes of hypophosphatemic osteomalacia
X-linked
Autosomal dominant
With hypercalciuria
Oncogenic osteomalacia

There is an increasing prevalence of vitamin D deficiency in many countries, even in those close to the equator, and those with abundant sunlight [22]. The at-risk population includes the elderly with little exposure to sunlight as well as patients with poor absorption including those with celiac disease and those submitted to gastrointestinal bypass surgery. Likewise, individuals living in cold weather climates, and women who wear clothes that cover almost the entire body area, are also predisposed to hypovitaminosis D [19].

The main histological findings are an excessive accumulation of bone matrix that is not, or only poorly, mineralized, decreased bone volume, increased accumulation of osteoid, and increases in the osteoid thickness of bones and the surface area [23].

### Clinical Manifestations

Osteomalacia may be asymptomatic. When symptomatic, general symptoms include chronic bone and muscle pain, weakness, fatigue, difficulty in walking, and a high risk of fractures due to bone fragility. Deformities related to the softening of the adult skeleton include kyphosis, pectus carinatum, a decrease in stature, genu varum, and acetabular protrusion [23].

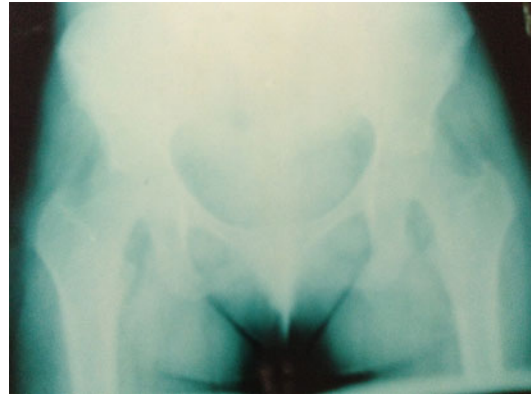
Bone pain seems to be caused by hydration of the demineralized bone matrix beneath the periosteum, which is extended, causing compression of nerve terminals. It is usually persistent, diffuse, and symmetrical, starting in the lower back and spreading to the pelvic girdle, hip, and ribs. Pain on palpation of these sites is an important clinical sign. Muscle weakness is usually proximal and associated with hypotonia, atrophy, and discomfort during movement [18].

### Diagnosis

The most characteristic laboratory findings are a lower serum calcium level, a decrease in urinary calcium levels, hypophosphatemia, and increased levels of alkaline phosphatase (ALP) (Table 26.6). Increased ALP activity is the most frequent and

**Table 26.6** Laboratory findings in nutritional osteomalacia

Laboratory results for osteomalacia	
Elevated PTH	100 %
25 (OH) Vitamin D < 15 ng/ml	100 %
Elevated alkaline phosphatase	95 %
Low urinary calcium	87 %



**Fig. 26.1** Looser's zone at the right pubis in a 32-year-old woman with hypophosphatemic osteomalacia

earliest marker for osteomalacia, and reflects the activity of the osteoblast, which forms the demineralized matrix [24]. The key test for the diagnosis of vitamin D deficiency is the demonstration of decreases in serum 26OHD [25].

PTH may be typically increased. As vitamin D deficiency increases, the hypersecretion of PTH leads to bone remodeling and endocortical bone reabsorption, resulting in cortical bone loss and increased risk of fractures. In addition, biochemical markers for bone turnover may be increased [18].

On X-rays, the most characteristic feature is the Looser's zone, a band adjacent to the periosteum which represents a stress fracture (cracks without repetitive posttraumatic displacement). It occurs most commonly in the ribs, pubis, and scapula (Fig. 26.1). This is in contrast to the fissures that occur in the long bones in Paget's disease [25]. Bone scintigraphy usually shows areas of focal increases in MDP uptake (Fig. 26.2). Bone mineral density is usually decreased, mainly in the cortical [18].



**Fig. 26.2** Bone scintigraphy in a 52-year-old woman with primary hyperparathyroidism and osteomalacia. Serum 25OHD: 8 ng/ml

Although the diagnosis of osteomalacia can be carried out on the basis of clinical and laboratory findings, transiliac bone biopsy, with tetracycline labeling, can help make a definitive diagnosis. This takes less than 30 min, under local anesthesia, with minimal discomfort to the patient. The specimen should be stored in 70 % alcohol and sent to a specialized laboratory for histomorphometric studies. The characteristic finding is impaired mineralization with an absent two-band tetracycline label [26].

Low serum 25OHD levels, increased FGF23 levels, and the presence of hypophosphatemia are reliable biomarkers for tumor-induced osteomalacia (TIO). FGF 23 is normally secreted by osteocytes and is an important regulator of phosphate homeostasis due to its action in the kidneys. It may also be secreted ectopically by mesenchymal tumors which are usually benign, typically very small, and difficult to locate. In fact patients with hypophosphatemic osteomalacia who have no family history for the disease should be screened for TIO. Whole-body Tc-99

Sestamibi or I-111-pentetreotide scintigraphy as well as FGD-PET or scintigraphy may be employed, followed by computerized tomography (CT) and/or magnetic resonance imaging (MRI) of the suspected lesions in an attempt to localize the tumor [27].

Selective venous sampling for FGF-23 measurements may be needed as a localizing procedure especially when multiple sites are identified by imaging examinations. It is also useful when a high degree of certainty is necessary for the location of the tumor before surgery [28].

## Treatment

Vitamin D is effective in the treatment of nutritional osteomalacia, or for malabsorption.

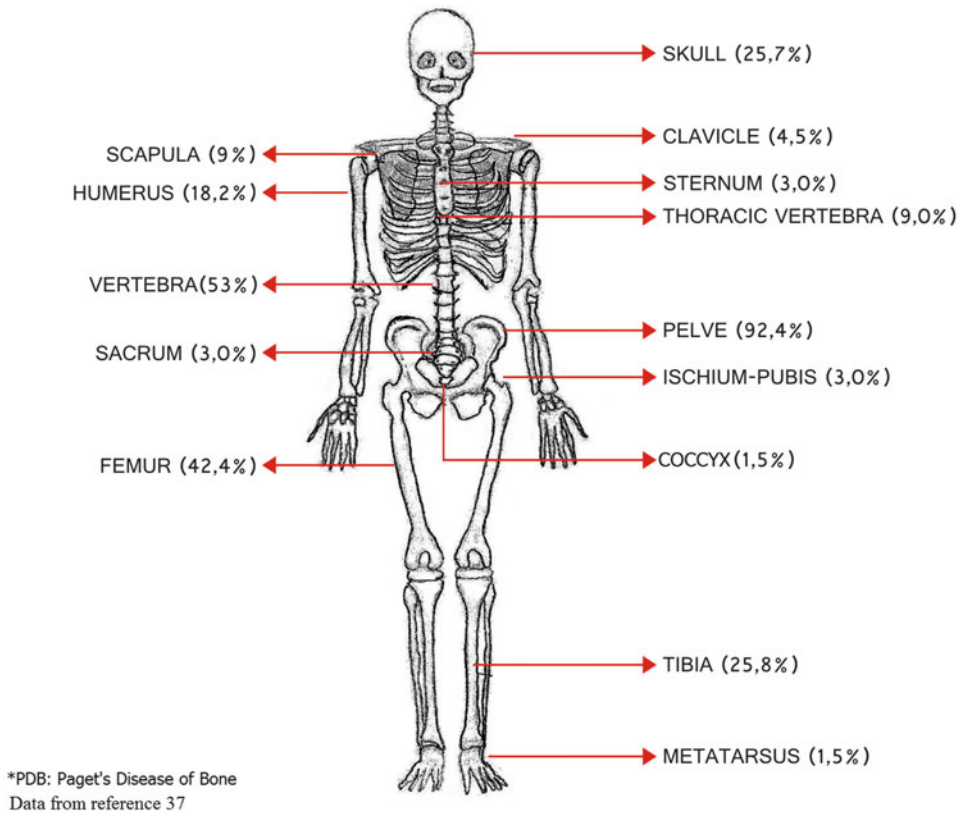
In general, 50,000 units of cholecalciferol (vitamin D3) are given once a week for 8 weeks, followed by an adjustment based on 25OHD levels. Bone biopsy may be performed to confirm that osteomalacia has been cured before starting antiresorptive or anabolic agents used for treating residual associated osteoporosis [29].

TIO is treated with a phosphate supplement (1–3 g/day of elemental phosphorus), along with vitamin D, until the tumor has been identified and excised [27]. There are reports of successful treatment of TIO with percutaneous, CT-guided, ethanol and cyoablation [30].

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## Paget's Disease of Bone

Paget's disease of bone (PDB) was first described in 1877 by an English physician, Sir James Paget. It is a chronic skeletal disease characterized by increased osteoclastic activity that leads to increased bone reabsorption [31]. There is a compensatory increase in the rate of newly formed bone. The rate of change in skeletal remodeling leads to architectural modifications characterized by nonlamellar excessive more vascularized bone formation which is less compact than normal bone. This disease may be localized, monostotic, or polyostotic, and the main sites affected are vertebrae, long bones of the lower limbs, pelvis, and skull (see Fig. 26.3) [32].



**Fig. 26.3** Sites of bone involvement in PDB

## Pathogenesis

Osteoclasts are derived from mononuclear precursor cells of monocytic-macrophage lineage, which fuse to form multinucleated osteoclasts, and are then activated to carry out bone resorption. Both local and systemic factors in the bone microenvironment are important for regulating the formation and activation of osteoclasts. In particular, the receptor activator of the nuclear factor- $\kappa$ B ligand (RANKL), a member of TNF superfamily, is an important regulator of osteoclast differentiation. Most of the factors, including  $1.25\text{-(OH)}_2\text{D}_3$ , IL-1, IL-11, and the parathyroid hormone, promote indirect osteoclast activation by binding to stromal marrow cells and inducing the expression of RANK in its ligand [33, 34].

There are at least seven mapped genetic loci associated with Paget's disease; the best documented is the mutation in the P392L in SQSTM1 (PDB3 Gene map locus 5q35) [35].

Patients without mutations in the SQSTM1 gene seem to have a susceptibility to genetic polymorphisms in regions of the following genes: CaSR, ESR1, TNFRSF11B (OPG), TNFRSF11A (RANK), CSF1 (M-CSF), OPTN, TM7SF4 (DC-STAMP), VCP, NUP205, RIN3, PML, and GOLGA6A, resulting in increased risk for development of PDB. The nature of these genes shows that Paget's disease is caused by the deregulation of osteoclastogenesis [36].

In situ hybridization studies and immunohistochemical analysis suggest the possibility of infection of osteoclasts by a virus, particularly

## Prevalence Studies on PDB Worldwide



**Fig. 26.4** Geographical distribution of Paget's disease worldwide

paramyxovirus, as a contributor etiological factor of PDB [32]. The identification of genetic mutations involved in osteoclastogenesis, and characterization of the nongenetic factors that may be involved, appears to be important in developing ways to understand and control the exaggerated bone remodeling in Paget's disease.

### Histopathology

Osteoclasts with Paget's disease are multinucleated and excessive in numbers. Increased bone turnover results in abnormal deposition of lamellar bone inserted into the bone tissue. The bone looks disorganized, with thickened trabeculae surrounded by numerous enlarged and multinucleated osteoclasts. The disorganization of the bone tissue leads to increased bone volume, resulting in the manifold complications of the disease. The normal bone marrow is replaced by a large amount of vascular tissue.

### Epidemiology

Geographical distribution is variable, the disease being more common in England, the USA, Australia, and New Zealand, but rare in Scandinavia and Asia (see Fig. 26.4). In Brazil, it is found predominantly in locations with a long-standing history of European colonization as in the city of Recife. In this location the prevalence reaches 0.7 % in people over 45 years of age [32, 37].

### Clinical Manifestations

Paget's disease is usually asymptomatic and discovered incidentally. The main clinical manifestations are bone pain, fractures, skeletal deformities, and secondary arthritis. In most cases, PDB may be diagnosed from the combination of symptoms, radiological findings, and increased concentration of biochemical markers for bone remodeling.

Juvenile Paget's disease is an extremely rare autosomal recessive disease, characterized by deafness in infancy, fractures, and deformities as the result of generalized bone turnover, normally due to deficiencies in osteoprotegerin (the decoy receptor for the RANK) gene [32].

## Diagnosis

PDB can be diagnosed when high serum ALP activity is found, or by routine X-ray examination [38].

Other bone turnover markers are often elevated in active disease, such as serum C-telopeptide (CTx), or urinary N-telopeptide (NTx). Serum calcium and phosphorus are normal in most patients. Hypercalcemia or hypercalciuria can occur in immobilizations or fractures [39].

Plain radiography and bone scintigraphy are useful in patients suspected of having PDB. The radiological findings may be diagnostic, showing typical irregular areas of osteosclerosis with adjacent areas of osteolysis, reflecting abnormal bone turnover characteristic of the disease. The osteolytic lesion that is seen in the skull in the early stages of the disease is known as *osteoporosis circumscrita*. Bone scintigraphy may be more sensitive, albeit less specific, than plain X-rays, especially early in the disease. Computed tomography and magnetic resonance imaging may be useful in unusual lesions, when the diagnosis of malignancy is likely [40].

It is important to obtain a baseline bone scan in all patients with PDB to document the extent and location of lesions, since the sites involved rarely change over time. Radiography should also be performed on the involved sites to identify musculoskeletal consequences of the disease, such as fractures, potentially malignant lesions, osteoarthritis, or other bone abnormalities [40].

Bone biopsy may be useful in atypical cases, as in young adults specially from countries with a low prevalence of the disease. Nonetheless, in suspected localized lesions without characteristic radiographic findings, bone aspiration sometimes shows the characteristic giant osteoclasts [41].

## Treatment

The objective of treatment is to relieve pain, restore normal bone metabolism, decrease bone vascularization, and prevent future complications such as bone deformities, secondary osteoarthritis, fractures, and compression of nerve structures [42].

Patients whose symptoms are caused by active Paget's disease (often associated with elevated ALP) should be treated. The most common symptom is bone pain in pagetic sites, causing headache, or pain in the back, joints, or limbs. Asymptomatic PDB is detected in imaging studies performed for other reasons (e.g., nephrolithiasis) or by the observation of elevated levels of ALP. The main indication for treatment of asymptomatic patients is biochemically active disease at sites where complications may occur (e.g., skull, spine, and bones adjacent to joints). In other sites, consider treatment if the AP is two to four times above the upper limit of normal. Other indications for treatment of asymptomatic patients include planned surgery for active pagetic sites (for the purpose of reducing bone turnover and vascularization, thus minimizing blood loss during the procedure) and the rare development of hypocalcaemia in association with the immobilization of patients with polyostotic disease. If such asymptomatic patients do not meet the above criteria for treatment, they should be followed up annually to assess disease progression [43].

Calcitonin was the first inhibitor of osteoclast activity to be used in the treatment of PDB. Nowadays it is used infrequently. It suppresses bone turnover and relieves pain, but is more expensive and less effective, and presents more side effects (nausea, metallic taste, and flushing) than bisphosphonates. The initial dose is 100 units/day, subcutaneously tapering to 50 units/day.

Bisphosphonates are considered the treatment of choice for PDB. They bind to bone surfaces in regions of high resorption, reducing osteoclastic activity, thereby reducing the bone turnover. When taken orally, they are poorly absorbed, especially in the presence of food in the stomach. They should therefore be taken when fasting,



with water, 30–60 min before meals, or any other medications [42]. They may cause heartburn, dyspepsia, and esophageal ulcers, and should be used with caution in patients with gastritis or duodenitis. More rarely, they can also cause an acute febrile reaction, uveitis, rash, and osteonecrosis of the jaw [44]. Normal serum levels of calcium, phosphorus, and 25OHD should preferentially be present when bisphosphonate therapy is initiated. Calcium should be provided (1,200 mg/day, preferably through a nutritional diet), along with vitamin D (800–2,000 units/day), in all patients undergoing treatment.

Etidronate was the first bisphosphonate to be used for Paget's disease, beginning in 1971. The newer and more potent bisphosphonates have proven more effective, leading to a longer period of remission [42]. Oral alendronate is more effective than etidronate. In a regimen of 40 mg/day for 6 months, it leads to a 77 % decrease in ALP levels, versus 44 % for etidronate [45]. Risedronate leads to similar results, with 30 mg daily doses given orally for 2 months. It should not be used in patients with CrCl < 30 ml/min [46]. Pamidronate is well tolerated and easily administered in hospitals or clinics, using 2–6-h IV infusions of 30–90 mg, diluted in 500 ml of 0.9 % saline, or 5 % glucose solution [47].

Zoledronic acid (zoledronate) has proven to be the most potent bisphosphonate for the treatment of PDB. It is 10,000 times more potent than etidronate and 100 times more potent than pamidronate [48]. It can be administered in 5 mg, IV infusions, for a shorter time (15–30 min) and in a smaller volume of at least 100 ml (saline or glucose). Hypophosphatemia, hypocalcaemia, and hypokalemia, as with other IV bisphosphonates, may occur, specially in patients with vitamin D deficiency at the time of infusion, as well as fever, chills, myalgia, and arthralgia [49, 50]. Zoledronic acid should also not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) [44] (Table 26.7). In clinical trials comparing oral and intravenous bisphosphonates, side effects, mainly gastrointestinal, were more prevalent when the oral route was used [48].

Indications for restart treatment with bisphosphonates depend on increasing evidence of

**Table 26.7** Bisphosphonate regimen Paget's disease

Medication	Dosage	Time period
Etidronate	400 mg/day (Oral)	6 months
Alendronate	40 mg/day (Oral)	6 months
Risedronate	30 mg/day (Oral)	2 months
Pamidronate	60–90 mg/dose (IV)	Every 3 months
Zoledronate	5 mg (IV)	Single injection

abnormal bone metabolism, determined by serial measurements of ALP, radiological progression of the disease, or recurrent pain. Increased ALP alone is not always an indication for retreatment. For retreatment, the dose and duration of therapy are the same as the initial treatment [43].

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## Part I: Clinical Stages of DM

Patients who ultimately develop DM pass through a spectrum of clinical stages during its progression (Table 27.1). Initially, glucose regulation is normal, and patients remain normoglycemic even if they are subjected to an OGTT. This stage is followed by a variable period of impaired glucose regulation, also known as prediabetes. This can be characterized as impaired fasting glycaemia (IFG), or impaired glucose tolerance (IGT). Prediabetes itself confers increased cardiovascular risk and retinopathy. Patients with prediabetes have 5–10 % [1] risk of progression to actual DM annually, compared to 0.7 % [1] in normoglycemic people. Once DM develops, lifestyle modification or oral hypoglycemic agents (OHGAs) may be sufficient for some patients, depending on the type of DM. On the other hand, some may require insulin for survival or control.

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## Part II: Classification of DM

Though DM was recognized several centuries ago, it was *HP Himsworth* who first proposed that DM could be differentiated into insulin-sensitive and insulin-insensitive types in 1936 [2]. *J Bornstein* and *RD Lawrence* found insulin bioactivity in the plasma of people with maturity-onset DM but not in juvenile-onset DM [3]. *SA Berson* and *RS Yalow* conclusively demonstrated this distinction by originating insulin radioimmunoassay [4]. This formed the basis of the initial classification of DM. During that time, patients with DM were classified according to the age of onset into juvenile-onset and maturity-onset subtypes. Juvenile-onset DM is insulin-sensitive, and maturity-onset DM is insulin-insensitive. The WHO Expert Committee on Diabetes made some changes in 1980 [5]. This classification separates DM into two main categories based on insulin dependency: insulin-dependent (type 1 DM) and non-insulin-dependent (type 2 DM). This was a preferred classification as the age of DM onset did not necessarily correlate with insulin dependency. In addition, the WHO classification also included a third category termed other specific causes of DM. Causes of this category of DM include: genetic defects affecting  $\beta$ -cell function or insulin action, diseases of the exocrine pancreas, endocrinopathies, and drugs. There was also a fourth category termed gestational DM (GDM) that described any form of hyperglycemia first detected during pregnancy. An entity called

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**Table 27.1** Clinical stages and etiologic types of DM

	Prediabetes		Diabetes	
	Normal	Insulin not needed	Insulin needed for control	Insulin needed for survival
Type 1 DM	←————→			
Type 2 DM	←————→			
Other specific types	←————→			
Gestational DM	←————→			

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malnutrition-related DM was introduced into the WHO classification in 1985, but was later removed due to inconclusive evidence of effects of malnutrition or protein deficiency on DM [6]. ADA proposed further changes to this classification in 1997 [7] (Table 27.2). Firstly, the terms insulin-dependent DM and non-insulin-dependent DM were eliminated, but type 1 DM and type 2 DM were retained. This was because many type 2 DM patients with progressive  $\beta$ -cell failure would require insulin therapy eventually and hence the term non-insulin-dependent DM might seem contradictory. Secondly, there was an inclusion of 2 subtypes of type 1 DM: type 1A, if it was immune-mediated; and type 1B, if it was idiopathic. This classification was subsequently adopted by WHO in 1999 as well, and is still in use.

However, assigning a type of DM to a patient frequently depends on his/her phenotype, and the circumstances present at the time of diagnosis. Sometime, the type of DM may not be evident at diagnosis. And many patients with DM do not easily fit into a single class. These will be illustrated in some of the case discussions below.

### Case 1

*A 19-year-old student with no past medical history, was admitted for diabetic ketoacidosis (DKA), precipitated by urinary tract infection. She had been lethargic, with weight loss, polydipsia, and polyuria for 2 months. Prior to her admission, she complained of 3 days' history of fever, dysuria, frequency, and abdominal pain. She did not have any family history of DM. She*

*was of slim built, with a body mass index (BMI) of only 17.3 kg/m<sup>2</sup>.*

*Laboratory investigations on admission:*

*Total white cell count: 16.4 × 10<sup>3</sup> U/L (4–10)*

*Serum sodium: 128 mmol/L (135–145)*

*Serum glucose: 34.5 mmol/L (3.1–7.8)*

*Serum bicarbonate: 13.8 mmol/L (19–31)*

*Serum creatinine: 171  $\mu$ mol/L (65–125)*

*Arterial blood pH: 7.23 (7.35–7.45)*

*Serum ketones: 4.6 mmol/L (<0.6)*

*Glycated HbA1c: 9.2 %*

*Glutamic acid decarboxylase (GAD) antibody: 117.4 U/mL (0–0.8)*

*Islet cell antibody (ICA): negative*

*Urine microscopy: 450 white blood cells*

This is a case of a newly diagnosed type 1 DM, presenting with diabetic ketoacidosis. Type 1 DM accounts for 5–10 % of all DM cases. It is due to immune-mediated  $\beta$ -cell destruction, resulting in insulin deficiency, leading to hyperglycemia and lipolysis (and hence, ketoacidosis). The rate of  $\beta$ -cell destruction is variable, being rapid in some individuals, especially infants and children, and slower in adults. Like Case 1, type 1 DM is usually diagnosed before 30–40 years of age, most commonly during childhood or adolescence. However, type 1 DM occurs throughout life and can be misdiagnosed as type 2 DM when it presents in the middle-aged population. The lean body habitus of Case 1 is also typical of a patient with type 1 DM. Type 1 DM is usually characterized by the presence of anti-GAD, anti-islet cell, or anti-insulin antibodies, which reflect the autoimmune processes that cause  $\beta$ -cell destruction. Patients who have one or more of these antibodies can be subclassified as type 1A (i.e., immune-mediated) diabetes. This accounts

**Table 27.2** Etiologic classification of DM

Type 1DM
<ul style="list-style-type: none"> <li>• 1A: autoimmune</li> <li>• 1B: idiopathic</li> </ul>
Type 2 DM
<i>Other specific types of DM</i>
<ul style="list-style-type: none"> <li>• Genetic defects of <math>\beta</math>-cell function: <ul style="list-style-type: none"> <li>MODY types 1-6</li> <li>Mitochondrial DNA</li> </ul> </li> <li>• Genetic defects in insulin action: <ul style="list-style-type: none"> <li>Type A insulin resistance</li> <li>Leprechaunism</li> <li>Lipoatrophic diabetes</li> <li>Rabson–Mendenhall syndrome</li> </ul> </li> <li>• Disorders of the exocrine pancreas: <ul style="list-style-type: none"> <li>Pancreatitis</li> <li>Pancreatic neoplasm</li> <li>Pancreatic surgery</li> <li>Cystic fibrosis</li> <li>Hemochromatosis</li> </ul> </li> <li>• Endocrinopathies: <ul style="list-style-type: none"> <li>Cushing’s syndrome</li> <li>Acromegaly</li> <li>Pheochromocytoma</li> <li>Hyperthyroidism</li> <li>Glucagonoma</li> <li>Somatostatinoma</li> </ul> </li> <li>• Medication-induced: <ul style="list-style-type: none"> <li>Glucocorticoids</li> <li>Nicotinic acid</li> <li>Pentamidine</li> <li>Diazoxide</li> <li>Phenytoin</li> <li><math>\beta</math>-Adrenergic agonists</li> <li>Thiazides</li> <li><math>\alpha</math>-Interferon</li> </ul> </li> <li>• Infections: <ul style="list-style-type: none"> <li>Congenital rubella</li> <li>Cytomegalovirus</li> </ul> </li> <li>• Uncommon forms of immune-mediated diabetes: <ul style="list-style-type: none"> <li>“Stiff-man” syndrome</li> <li>Anti-insulin receptor antibodies</li> </ul> </li> <li>• Other genetic syndromes sometimes associated with diabetes: <ul style="list-style-type: none"> <li>Down syndrome</li> <li>Klinefelter syndrome</li> <li>Turner syndrome</li> <li>Wolfram syndrome</li> <li>Friedreich ataxia</li> <li>Huntington chorea</li> <li>Laurence–Moon–Biedl syndrome</li> <li>Myotonic dystrophy</li> <li>Prader–Willi syndrome</li> <li>Porphyria cutanea tarda</li> </ul> </li> </ul>
Gestational DM

for 80–90 % of type 1 DM. Some patients, mainly non-whites, may not have any of these autoimmune antibodies and are subclassified as type 1B

(i.e., idiopathic) diabetes. Type 1 DM, especially type 1A, shows strong associations with specific haplotypes or alleles at the DQ-A and DQ-B loci of the human leukocyte antigen (HLA) complex. Despite the genetic predisposition, concordance rates for type 1 DM in identical twins are not significant [8]. Patients with type 1 DM require insulin for survival and to prevent DKA.

## Case 2

*A 26-year-old man was diagnosed with DM 5 years ago during a routine health screen. Both his parents developed DM in their 40s. He was overweight with a BMI of 28.3 kg/m<sup>2</sup> and waist circumference of 110 cm. He is currently on two oral hypoglycemic agents (metformin and sitagliptin). He does not suffer from any macrovascular or microvascular complications of DM.*

*Laboratory investigations during his latest outpatient clinic review:*

*HbA1c: 7.6 %*

*Triglycerides: 2.0 mmol/L (<1.7)*

*Low-density lipoprotein (LDL): 3.2 mmol/L (<2.6)*

*High-density lipoprotein (HDL): 0.9 mmol/L (1–1.6)*

This is a case of a young type 2 DM. Type 2 DM is the most common type of DM, accounting for more than 90 % of the cases. This form of DM is characterized by insulin resistance, leading to relative insulin deficiency. Like Case 2, most type 2 diabetics are overweight or obese, or at least have some central adiposity. Obesity itself aggravates insulin resistance. Though type 2 DM was traditionally thought to occur only in older individuals, there is a growing incidence of type 2 DM in young adults due to the increasing prevalence of obesity in affluent countries. In contrast to type 1 DM, type 2 DM shows strong familial aggregation. DKA seldom occurs in this type of DM unless there is precipitant(s) such as infection. Type 2 diabetes is usually diagnosed late as it develops gradually and patients remain asymptomatic during the initial stages. Lifestyle modification and weight reduction decrease insulin resistance in these patients, thereby improving their glycemic control. Many of them may require OHGAs as well. The

**Table 27.3** Differences between type 1 and type 2 DM

	Type 1 DM	Type 2 DM
Frequency	5–10 % of all DM	>90 % of all DM
Etiology	Immune-mediated islet cell destruction, leading to absolute insulin deficiency; can be idiopathic	Insulin resistance with relative insulin deficiency
Age at presentation	Usually during childhood or adolescence	Usually after middle age
Body habitus	Usually slim	Usually overweight
Family history of DM	Usually no	Usually yes
Treatment	Need insulin at diagnosis	Usually treated with diet control or OHGAs, but may require insulin later

United Kingdom Prospective Diabetes Study (UKPDS) [9] had shown that despite lifestyle modification and pharmacotherapy, there is progressive loss in  $\beta$ -cell function, and insulin may ultimately be needed for control of these patients' glycemic deterioration (Table 27.3, differences between type 1 and 2 DM).

### Case 3

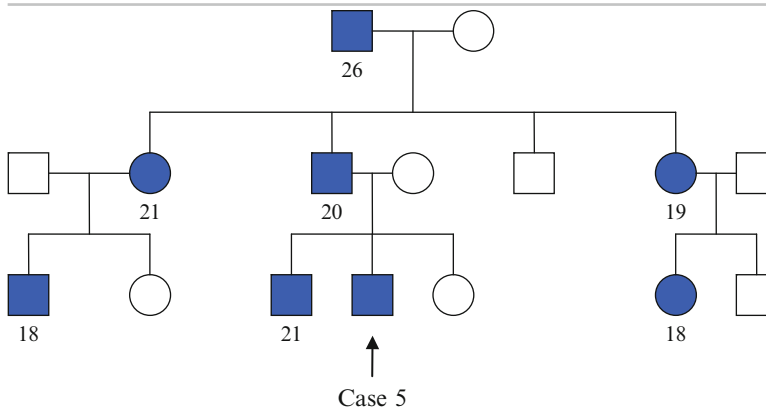
*A 40-year-old man with generalized vitiligo, was diagnosed with DM 2 years ago when he was admitted to hospital for lower limb cellulitis. There was no family history of DM. He was of slim built with a BMI of 18.6 kg/m<sup>2</sup>. His physician started him on OHGAs (metformin and gliclazide) with good improvement in his glycemic control. However, despite compliance to diet and increasing doses of his OHGAs (metformin, gliclazide, glucobay), he was unable to maintain his HbA1c within 7 %. His fasting C-peptide was 0.1 nmol/L, indicating inadequate pancreatic  $\beta$ -cell reserve. And his anti-GAD antibodies and ICA were both positive. He was started on insulin 15 months after his presentation, with prompt improvement in his glycemic control.*

Case 3's age of presentation and the absence of insulin dependence at diagnosis seemed to suggest that he had type 2 DM. However, he had several features more typical of type 1 DM, namely, his lean body built, the lack of family history of DM, presence of GAD and ICA antibodies, as well as the rapid progression to insulin dependency. The presence of vitiligo also suggested he has a predisposition for autoimmune

conditions. This is an atypical form of DM known as type 1.5 DM, latent autoimmune diabetes of adult onset (LADA), or autoimmune diabetes in adults with slowly progressive  $\beta$ -cell failure (ADASP). LADA is defined by three features, including: adult age at diagnosis (usually above the age of 30), the presence of diabetes-associated autoantibodies, and a delay in the progression to insulin dependency (more than 6 months, up to 10–12 years) [10]. Case 3 fulfilled all these three criteria. Studies have shown that among patients with phenotypic type 2 DM, LADA occurs in 10 % of people above 35 years old and 25 % below that age [11]. It is important to distinguish patients with LADA from type 2 DM, as treatment of choice is early insulin therapy to prevent the progression to complete  $\beta$ -cell failure from glucose toxicity. Sulfonylureas, which are commonly used to treat type 2 DM, have been thought to promote  $\beta$ -cell failure due to their stimulatory effect of insulin secretion by the pancreas, and should generally be avoided in LADA [12].

### Case 4

*A 36-year-old overweight Afro-American, diagnosed with type 2 DM 3 years ago (anti-GAD and ICA negative, HbA1c 8.5 %), non-compliant to his treatment with metformin and gliclazide, was admitted to the hospital with DKA. There was no evidence of infection or other precipitants for his DKA. He was switched to biphasic insulin (30 units pre-breakfast and 20 units pre-dinner) upon his discharge from hospital. However, he started experiencing hypoglycemic events at*

**Table 27.4** Family tree showing people with DM in Case 5's family

Note: The numbers indicate the age of onset of DM in affected family members

home which persisted even after he had progressively reduced the dosage of biphasic insulin to 18 units pre-breakfast and 8 units pre-dinner. His fasting C-peptide was 0.8 nmol/L, indicating presence of sufficient pancreatic reserve. He was subsequently switched back to sustained release OHGAs of metformin 1,000 mg twice daily and gliclazide 60 mg once daily. His hypoglycemic episodes resolved and his overall glycemic control improved with his HbA1c dropping to 7.2 %.

This case illustrates a seemingly typical young type 2 DM in an overweight individual. However, it is unusual for patients with type 2 DM to develop DKA, particularly in the absence of precipitants. This is an example of another atypical form of DM, known as ketosis-prone type 2 DM. It is more common in Afro-American and Hispanic patients. Hence, it is also known as Flatbush DM, in recognition of the place from where many of the original cases came from [13]. Patients with ketosis-prone type 2 DM are usually young to middle-age overweight individuals with history of acute, unprovoked episodes of DKA. Unlike type 1 DM, DKA in these patients is not due to irreversible  $\beta$ -cell damage, but hypothesized to be due to increased susceptibility to  $\beta$ -cell desensitization due to glucose toxicity [14]. Upon reversal of glucose toxicity with insulin therapy, the  $\beta$ -cell function partially recovers and patients should be converted to OHGAs to prevent hypoglycemia. Basal and stimulated C-peptide levels of more than 0.33 nmol/L and 0.5 nmol/L respectively

shortly after presentation of DKA, as well as more than 0.5 nmol/L and 0.75 nmol/L respectively during follow-up, have been shown to be good predictors of remissions [13–15]. It is advisable to keep patients with ketosis-prone type 2 DM on OHGAs (usually low dose sulfonylurea and metformin), as normoglycemic remission periods are significantly shortened (to within 2 years) compared to if they are treated with diet control alone after discontinuation of insulin therapy [15–17].

### Case 5

A 19-year-old student presented with polydipsia and polyuria of few months and was diagnosed with DM. In view of his young age of presentation and lean built (his BMI is 19.8 kg/m<sup>2</sup>), he was treated as for type 1 DM and was commenced on subcutaneous insulin therapy. During one of his outpatient reviews, it was realized that he has a very significant family history of young-onset DM (Table 27.4, family tree showing affected individuals). He underwent genetic testing for maturity onset diabetes of the young (MODY) which confirmed mutation in HNF1 $\alpha$ , one of the transcription factors that affect  $\beta$ -cell development and function. He was switched to gliclazide and has maintained satisfactory glycemic control since then.

MODY is early onset autosomal dominant DM that is associated with  $\beta$ -cell dysfunction resulting from specific mutations in genes encoding the



glucose-sensing enzyme glucokinase (GCK) or one of the transcription factors. It can be subclassified to types 1–6, according to the different gene involved. There is a seventh type called MODYx, which includes cases which the genetic mutation is still unknown (Table 27.5, subtypes of MODY). Clinical presentation (including age of onset, severity and progression of hyperglycemia) varies greatly depending on the underlying genetic mutation, but affected patients are non-insulin-dependent at the onset of the disease. In addition, they are usually of lean body habitus with no or minimal insulin resistance.

Patients with glucokinase dysfunction MODY have mild fasting hyperglycemia (5.5–8.0 mmol/L) from birth. Their post-OGTT glucose excursion is often also very mild (increment of less than 4.6 mmol/L) [18]. They do not have symptoms of DM. As their hyperglycemia is mild, they generally do not require OHGAs and do not develop microvascular complications of DM, but will insulin treatment during pregnancy. In contrast, patients with transcription factor MODY (of which hepatic nuclear factor (HNF) 1 $\alpha$  is most common) are usually born with normal glucose regulation, but develop progressive  $\beta$ -cell dysfunction leading to DM between the age of 10–30 years old. At presentation, they usually have normal fasting plasma glucose, but markedly elevated post-OGTT glucose excursion. These patients often require pharmacological therapy and the first line treatment is sulfonylureas.

MODY should be considered in patients with DM diagnosed before 25 years old, who do not fully fit into the phenotypes of type 1 or 2 DM and who have a strong family history of young-onset DM. Differentiating this from type 1 DM is particularly important as these patients can often be effectively treated without insulin therapy.

Genetic testing is important, not only to guide appropriate treatment and predict clinical course, but also to provide genetic counseling for their families, since there is a 50 % risk of 1st degree relatives having the same gene mutation due to its autosomal dominant inheritance.

Mutations identified in the GCK, HNF1 $\alpha$  and HNF4 $\alpha$  genes include missense, nonsense, splicing, small deletions/insertions/duplications,

splice site and promoter region mutations [19, 20] Partial and whole deletions have also been reported in HNF1 $\alpha$  and GCK genes [21].

As mentioned previously, GCK gene mutations are associated with mild, stable hyperglycemia. A fasting glucose of 5.5–8 mmol/L and post OGTT glucose increment of less than 4.6 mmol/L, together with a family history of type 2 DM or GDM are strong indications for GCK gene analysis. The process involves sequencing of the promoter, exons 1A-10 and the splice sites of the GCK gene, and the dosage analysis for partial and whole gene deletion of GCK [22].

Genetic testing for HNF1 $\alpha$  gene involves sequencing the exons 1–10 and splice sites of HNF1 $\alpha$  gene, and dosage analysis for partial and whole gene deletions of HNF1 $\alpha$ . On the other hand, HNF4 $\alpha$  testing will require sequencing of the P2 promoter, exons 1d–10 and splice sites of HNF4 $\alpha$  gene, as well as dosage analysis for partial and whole gene deletions of HNF4 $\alpha$  [23].

## Case 6

*A 28-year-old primigravida, who was diagnosed with DM at the 26th week of pregnancy, had been overweight since childhood. Her BMI was 29.4 kg/m<sup>2</sup> before her pregnancy. Both her parents were diagnosed with type 2 DM in their 50s. Her fasting plasma glucose (FPG) done during her first antenatal consultation was 4.9 mmol/L. OGTT done during 26th week of gestation showed elevated 2-h plasma glucose of 9.2 mmol/L. She was started on insulin therapy for her GDM and subsequently delivered a healthy 3.2 kg baby boy at the 38th week of gestation. Results of OGTT done 8 weeks postpartum had reverted to normal.*

Gestational DM (GDM) is conventionally defined as glucose intolerance of any severity with its onset or first recognition during pregnancy [24]. It is not uncommon, as up to 10 % [25] of pregnancies are complicated by GDM. However, this definition does not exclude unrecognized DM that antedates pregnancy, which is a growing problem. In the recent years, studies have shown that it is important to distinguish

**Table 27.5** Comparison of the different subtypes of MODY

	MODY1 (HNF4 $\alpha$ )	MODY2 (GCK)	MODY3 (HNF1 $\alpha$ )	MODY4 (IPF1)	MODY5 (HNF1 $\beta$ )	MODY6 (NDI)	MODYx
Frequency	5 %	20 %	60 %	<1 %	5 %	<1 %	10 %
Chromosomal location	20q13.12	7p13	12q24.31	13q12.2	17q12	2q31.3	Not known
Onset	Early adulthood	Birth	Early adulthood	Early adulthood	Early adulthood	Adulthood	Not known
Severity	Can progress	Mild	Can progress	Not known	Can progress	Not known	Variable
Pathophysiology	$\beta$ -cell dysfxn	$\beta$ -cell dysfxn; glucose sensing disorder	$\beta$ -cell dysfxn	$\beta$ -cell dysfxn	$\beta$ -cell dysfxn; insulin resistance	Not known	$\beta$ -cell dysfxn
Microvascular complications	Often	Rare	Often	Not known	Often	Not known	Not known
Associated features	Low triglycerides	Low birth weight	Low renal threshold for glucose	Pancreatic agenesis	Renal cysts; renal failure	Not known	Not known

Note: IPF1 = insulin promoter factor 1; NDI = NeuroDI

pregnant women with undiagnosed preexisting DM from those who develop glucose intolerance during pregnancy. This is because the former group is at a higher risk of developing diabetic complications such as nephropathy and retinopathy during pregnancy [26]. Their newborns are also at higher risk of developing congenital anomalies [27]. There is a need for prompt treatment and close follow-up during pregnancy to ensure early restoration of normoglycemia. Hence, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommends that all women should be screened for their risk of development of GDM upon diagnosis of pregnancy [28]. These risk factors include: current glucosuria, obesity, previous GDM, known polycystic ovarian syndrome (PCOS), and family history of type 2 DM. Women with any of the above risk factors should have their FPG, random plasma glucose (RPG), or HbA1c checked. Preexisting or overt DM is diagnosed if the standard diagnostic criteria (to be covered in later part of this chapter) is met, i.e., FPG  $\geq 7.0$  mmol/L, HbA1c  $\geq 6.5$  %, or RPG  $\geq 11.1$  mmol/L. A positive RPG should be followed by FPG or HbA1c for the confirmation of DM. On the other hand, if FPG is  $\geq 5.1$  mmol/L but  $< 7.0$  mmol/L, the patient is diagnosed to have GDM. Patients with FPG  $< 5.1$  mmol/L should undergo a 75-g OGTT during their 24–28th weeks of gestation. GDM is diagnosed if FPG  $\geq 5.1$  mmol/L, 1-h plasma glucose  $\geq 10$  mmol/L, or 2-h plasma glucose  $\geq 8.5$  mmol/L. In view of her positive family history of type 2 DM and her body habitus, Case 6 belongs to the high-risk group. Her FPG done at the beginning of her pregnancy was normal. However, she developed GDM subsequently which was diagnosed on OGTT during 26th week of gestation. It is important to achieve tight glycemic control for GDM mothers during pregnancy, because the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [29] showed a continuous association between maternal glycemia and adverse perinatal outcomes below levels diagnostic of DM. These adverse perinatal outcomes include: congenital malformations, stillbirth, macrosomia (leading to increased risk of birth trauma), neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome

**Table 27.6** IADPSG diagnostic strategy/criteria and follow-up for GDM

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1st ante-natal visit:
Assess risk factors for DM
In high-risk women, check FPG, RPG, or HbA1c
<i>Overt/preexisting DM</i> if:
FPG $\geq 7.0$ mmol/L
RPG $\geq 11.1$ mmol/L (need to confirm DM by repeating FPG or HbA1c)
HbA1c $\geq 6.5$ %
<i>GDM</i> if:
FPG $\geq 5.1$ mmol/L, but $< 7.0$ mmol/L
At 24–28th weeks of gestation (if previous FPG $< 5.1$ mmol/L):
Perform 75-g OGTT
<i>GDM</i> if:
FPG $\geq 5.1$ mmol/L
1-h post OGTT $\geq 10$ mmol/L
2-h post OGTT $\geq 8.5$ mmol/L
6–8 weeks post-partum:
Repeat 75-g OGTT for women with GDM

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(as fetal hyperinsulinemia delays lung maturity by decreasing surfactant production). The treatment of choice for GDM is medical nutrition therapy +/- insulin therapy and patients need to be on seven-point capillary blood glucose monitoring. Long-acting insulin analogues such as detemir (Levemir) and glargine (Lantus) are not currently recommended, as they have not been extensively studied in pregnancy. It is also important to check patients' retinas and check for microalbuminuria each trimester, as DM retinopathy and nephropathy may progress during the course of pregnancy [26]. Women with GDM have a 35–60 % [30] risk of developing type 2 DM, hence an OGTT should be repeated 6–8 weeks postpartum. While Case 6 did not have DM on repeat OGTT, she continues to be at higher risk of developing GDM in any subsequent pregnancies and for type 2 DM in future (Table 27.6, IADPSG diagnostic strategy/criteria and follow-up for GDM).

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### Part III: Laboratory Diagnosis of DM

Among the diagnostic armamentarium used for DM, OGTT has traditionally been the test of choice. In some cases, FPG or RPG may be adequate for the diagnosis of DM. In recent years, there is increasing practice in the usage of HbA1c

**Table 27.7** ADA diagnostic criteria for prediabetes and DM

	FPG (mmol/L)	Post-OGTT (mmol/L)	HbA1c (%)
Normal	<5.6	<7.8	<5.7
Prediabetes			
• IFG	5.6–6.9	<7.8	5.7–6.4
• IGT	<7.0	≥7.8 to <11.1	
Diabetes	≥7.0	≥11.1 (or RPG of >11.1, with hyperglycemia symptoms)	≥6.5

not just for follow-up of patients' glycemic control, but for diagnosis of DM as well. The ADA diagnostic criteria of prediabetes and DM using these test modalities are shown in the Table 27.7 [31]. WHO adopts a similar criteria, apart from using a higher cut-off for FPG of 6.1 mmol/L for the diagnosis of IFG [32]. This was the previous cut-off value that ADA used before its review to lower it to 5.6 mmol/L in 2003. ADA advocated the inclusion of HbA1c as one of the tests used in the diagnosis of DM in 2009 [33]. This was supported by the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF), and subsequently by WHO [34]. In the absence of unequivocal hyperglycemia, the same diagnostic test should be confirmed by repeat testing. On the other hand, if a patient has been subjected to two different diagnostic tests and the results are discordant, the test with positive result should be repeated, and the diagnosis should be made based on the confirmed test. If the repeated value falls below the diagnostic cut-off, the patient should be followed up and have the test repeated in 3–6 months [31]. The various laboratory tests used in the diagnosis of DM are covered below.

### Serum Glucose and OGTT

The test for FPG requires patients to be fasted for minimum of 8 h. It is a simple and economical test. However, the blood specimen must be spun down quickly in the laboratory as there is steady loss of glucose with time even if fluoride blood tubes are used due to on-going glycolysis. This is because glucose consumption takes place within blood cells shortly after sampling, but fluoride inhibits glycolysis only in its more distal steps [35]. It has been estimated that glucose concentration

decreases 5–7 % (i.e., around 0.5 mmol/L) per hour [35, 36]. This rate may increase further in the setting of high ambient temperature [35, 36]. The pre-analytical variability of FPG is around 5–10 % [35]. In addition, FPG may vary according to the coexisting conditions of the patients (e.g., falsely high during sepsis).

OGTT also requires patients to be fasted for 8 h. A blood sample is taken at zero minute for plasma glucose before giving a glucose load (75 g of glucose in 300 ml of water to be consumed over 5 min). Plasma glucose is repeated after 120 min.

The diagnostic values of 7.0 mmol/L and 11.1 mmol/L for FPG and 2-h post-OGTT respectively were derived from studies that showed a linear increase in diabetic retinopathy at glucose levels beyond these two values [31].

### Glycated Hemoglobin (HbA1c)

HbA1c refers to degree of glycation of hemoglobin throughout the 120-day average lifespan of red blood cells (RBC), with the oldest cells being most glycated and the youngest, the least. The more recent the period of hyperglycemia, the greater the influence on HbA1c level. *Tahara* et al. had shown that the immediate past 30 days of hyperglycemia account for 50 % of HbA1c value, the next 30 days (30–60 days before) account for 25 %, and then 60–120 days before account for the remaining 25 % [37]. In the earlier years, HbA1c was not used for the diagnosis of DM as the assay lacked in standardization. However, HbA1c is now performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) [38] which is traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. The diagnostic cut-off HbA1c of

**Table 27.8** Conditions associated with falsely low/high HbA1c levels

Falsely low HbA1c	Falsely high HbA1c
<i>Associated with increased RBC turnover:</i>	<i>Associated with decreased RBC turnover:</i>
– Hemolysis	– Iron-deficiency anemia
– Hemorrhage	– Post-splenectomy
– Venesection	
– Hypersplenism	
– Treatment of iron-deficiency anemia	
– G6PD deficiency (with or without hemolysis)	
– Drugs, e.g., antiretrovirals, ribavirin, dapsone	
– Pregnancy	
Hemoglobinopathies, e.g., beta-thalassemia	

6.5 % is chosen, also because values above this has been shown to be associated with increased prevalence of diabetic retinopathy [33]. For many years NGSP had been the sole basis for improved harmonization of HbA1c assays. More recently, the International Federation of Clinical Chemists (IFCC) started a working group on HbA1c to introduce an international standardization program [39]. The HbA1c results by the IFCC reference system are reported in mmol/mol.

More and more clinicians are using HbA1c to diagnose DM because it is more convenient to perform as patients do not need to be fasted. There is greater pre-analytical stability (compared to plasma glucose testing), and lesser variations to stress and illnesses [40]. HbA1c correlates well with microvascular (and to a lesser extent, macrovascular) complications of DM. The estimated average glucose (eAG) can also be derived from HbA1c using this formula [41, 42]:  $eAG \text{ (mmol/L)} = (HbA1c \times 1.59) - 2.59$ . However, HbA1c is a more costly test and may not be available in certain developing countries. In addition, care must be taken in the interpretation of HbA1c results, as they can be misleading in patients with anemia, hemoglobinopathies, or other causes of abnormal red cell turnover (Table 27.8, causes of falsely low and high HbA1c values). HbA1c may also be

unreliable in patients who have recent blood transfusion [43]. Furthermore, it has been reported that glycation gap may exist, indicating possible variations in glycation between people despite exposure to the same ambient glucose [44]. *WH Herman* and *RM Cohen* showed that there are differences in HbA1c amongst people of different races and ethnic groups, with blacks having higher HbA1c values than whites across the continuum of glycemia [45]. Though the reasons behind these differences are not known, differences in red cell survival, extracellular-intracellular glucose balance, and nonglycemic genetic determinants of hemoglobin glycation have been postulated [45].

## Case 7

*A 62-year old man with end-stage renal failure on hemodialysis, was found on routine blood tests during dialysis, to have random blood glucose ranging from 10.6 to 14.1 mmol/L. He did not have any osmotic symptoms such as polydipsia and polyuria. His HbA1c was 5.6 %, but OGTT showed elevated FPG and 2-h post glucose load readings of 7.4 mmol/L and 12.8 mmol/L respectively. Does he have DM?*

This is a case with discordant HbA1c and OGTT results. HbA1c is an unreliable test in patients with significant renal impairment due to a few factors. The presence of carbamylated hemoglobin in patients with renal failure can interfere with some of the HbA1c assays, giving rise to falsely high HbA1c levels [46, 47]. On the other hand, uremia causes loss of RBC surface lipids, leading to reduced deformability of RBCs, resulting in shorter RBC survival, and hence falsely low HbA1c levels. This is particularly so in patients on hemodialysis [48]. In addition, many patients with renal failure are on erythropoietin therapy and this causes erythrocytosis which also gives rise to falsely low HbA1c levels. In view of these factors, plasma glucose is a more suitable test to use for the diagnosis of DM in patients with renal failure. On the same note, capillary blood glucose is also more reliable in the assessment of glycemic control in these patients, compared to HbA1c.

## C-Peptide

Like insulin, connecting peptide (C-peptide) is a cleaved product of pro-insulin. It is secreted in equimolar concentrations with insulin into the circulation, but has no definite effects on carbohydrate metabolism. Its plasma half-life is 30 min, much longer than that of insulin (around 4 min). Unlike insulin, it is not extracted by the liver, and is excreted almost entirely by the kidneys. It also has constant peripheral clearance at different plasma concentrations and during changes in plasma glucose concentrations. C-peptide is not part of the diagnostic armamentarium for DM, but in view of the characteristics mentioned above, it is commonly used as a marker of  $\beta$ -cell function or reserve, as it reflects endogenous insulin production of the pancreatic islet cells. A fasting C-peptide of  $<0.2$  nmol/L has been shown to reflect severe insulin deficiency, indicating the need for exogenous insulin therapy [49]. C-peptide can be stimulated by the administration of 1 mg of glucagon intravenously. Its levels are measured at baseline, and 6 and 10 min after intravenous glucagon. Normal stimulation of C-peptide is a 150–300 % elevation over basal levels [50]. A stimulated C-peptide of  $<0.5$  nmol/L is suggestive of severe insulin deficiency [49].

Even though C-peptide cannot be used as a diagnostic tool for DM, it is useful in cases whereby the type of DM is not clear as it can help clinicians decide if these patients require insulin therapy. This has been illustrated in Cases 3 and 4 earlier in this chapter.

## Autoantibodies

There are four main autoantibodies associated with type 1 DM, namely, islet cell autoantibodies (ICA), glutamic acid decarboxylase autoantibodies (GAD), islet antigen-2 autoantibodies, and insulin autoantibodies [51]. They are not diagnostic tests for DM, but can help to differentiate type 1 DM from other types of DM, as up to 90 % of patients with type 1 DM have at least one positive autoantibody. However, the prevalence of

positive autoantibodies is dependent on ethnic groups, with largest prevalence among Caucasians. In certain non-white populations, the prevalence may be as low as 40–50 % [52].

Autoantibodies against GAD are most commonly to the GAD65 isoform (GAD65Ab). GAD65Ab are more sensitive than ICA autoantibodies. Unlike ICA autoantibodies, they remain detectable for many years even after substantial loss of  $\beta$ -cell function [53]. In addition, their detection rate increases with age in new onset type 1 DM. This is in contrast to insulin autoantibodies whose predictive value for type 1 DM seems to be higher among younger children, possibly due to a higher rate of  $\beta$ -cell destruction. Insulin autoantibodies are detectable in 90 % of children who have type 1 DM before the age of 5, compared to only 40–50 % of adolescents older than 15 years old [54]. Islet antigen-2 autoantibodies are detected in about 60–70 % of patients with new-onset DM [55]. They are often preceded by insulin autoantibodies, GAD65Ab and ICA autoantibodies respectively [56], and the frequency decreases with increasing age of onset.

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## Conclusion

There is a myriad of different causes of DM. Even though the common denominator of all types of DM is hyperglycemia, it is important to ascertain the etiology behind each patient's DM in order to understand/predict its clinical course so as to guide clinicians in the management of these patients. Age at onset, clinical presentation, patients' phenotype and medical history, as well as family history of DM, play important roles in helping to clinch the diagnosis.

Though OGTT is traditionally used as the gold standard diagnostic test for DM, more clinicians are now switching to HbA1c. While this is generally a useful test following the worldwide standardization of the assay, clinicians should understand the limitations of the utilization of HbA1c as the diagnostic test for DM, and choose the patients who can benefit from this test wisely.

In patients whom the etiology of DM is not clear, it may be worthwhile checking the

C-peptide levels to have an estimation of  $\beta$ -cell reserve to assess if these patients require exogenous insulin therapy.

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### Diagnosis of Gestational Diabetes

The diagnosis and indeed the existence of gestational diabetes (GDM) has been a subject of controversy for many years. Historically, the first description of diabetes that had its onset during and symptomatically disappeared after the pregnancy was made by Bennewitz in 1824 [1]. However, it was not until the 1940s when Miller documented the increased frequency of prior adverse obstetric outcomes in women who later developed diabetes that recognition of GDM as an entity began to gain credence [2]. At that stage, it was considered to be a pregnancy-limited condition which resolved in the post-partum period [3]. Its importance as a form of “pre-diabetes” was recognized by O’Sullivan and Mahan in 1964 [4]. They identified GDM as a precursor and predictor of later permanent diabetes. These two important strands of the epidemiologic

importance of GDM have become increasingly interwoven since that time.

Current understanding of the pathophysiology of GDM includes two key components. These are the existence of pancreatic  $\beta$  cell dysfunction (generally inferred to be present before pregnancy) and the unmasking of this problem by the development of insulin resistance during pregnancy, which requires enhanced insulin production to maintain normoglycaemia. The etiologic factors underlying GDM, namely  $\beta$  cell dysfunction and insulin resistance, are not routinely measured in routine clinical practice, which relies on identification of their major consequence, hyperglycaemia, for diagnosis of GDM. This is generally measured under the additional stress of an oral glucose load, in the form of an oral glucose tolerance test (OGTT), which serves to unmask more subtle degrees of hyperglycaemia. The major effects of maternal hyperglycaemia are seen through stimulation of foetal growth by mild foetal hyperglycaemia and consequent foetal hyperinsulinemia as outlined by Pedersen and refined by Freinkel to include the role of other nutrients [5]. The Pedersen Hypothesis and modifications are represented in Fig. 28.1.

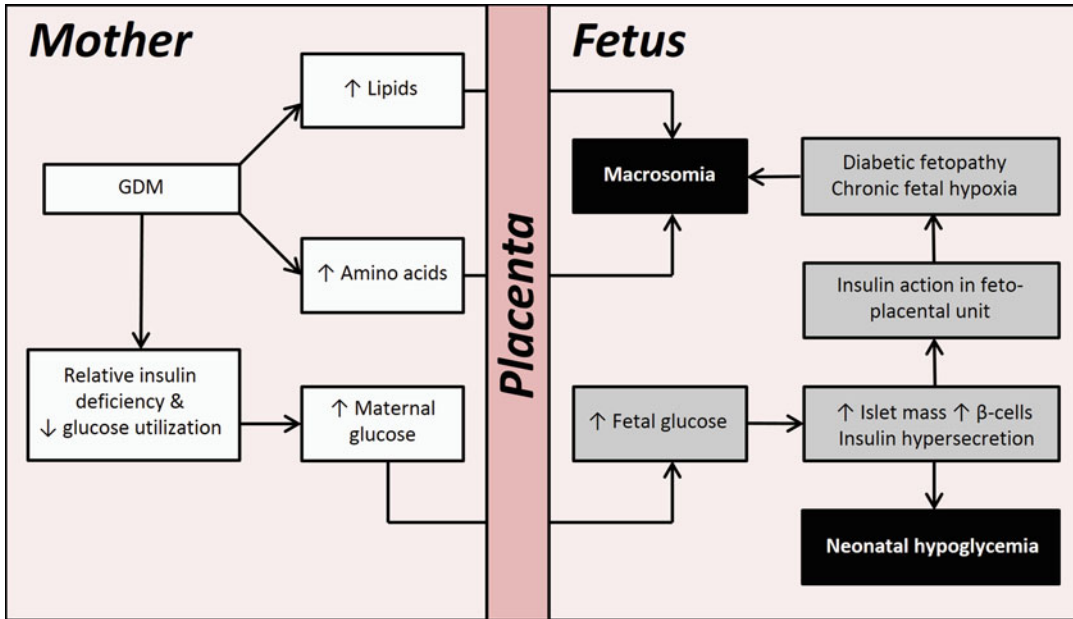
Prior diagnostic pathways and nomenclature for diagnosis of GDM have been heterogeneous. However, the recently published results of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study [6] and subsequent consensus development process auspiced by the International Association of Diabetes in Pregnancy Study Groups (IADPSG) [7] have led

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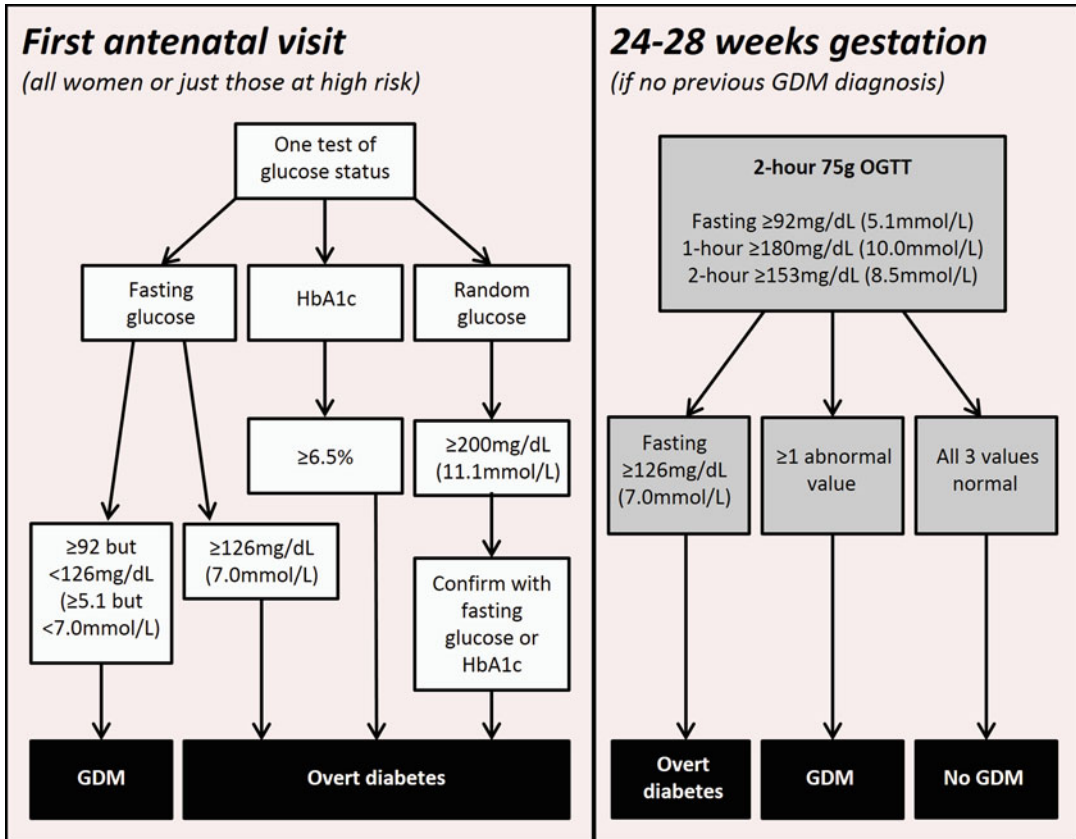
**Fig. 28.1** The Pedersen Hypothesis. “Maternal hyperglycemia begets foetal macrosomia” Modified by Freinkel to include nutrients other than glucose (lipids and amino acids)

to a clearer and more uniform approach, grounded primarily in the risk of adverse pregnancy outcomes associated with mild hyperglycaemia in pregnancy. The IADPSG criteria [7] will be the primary point of reference for diagnosis of GDM in this paper.

The HAPO study [6] demonstrated a continuous and essentially linear relationship between maternal glycaemia, measured during a three sample (fasting, 1 h, 2 h) 75 g OGTT performed between 24 and 32 weeks gestation and a series of clinically important pregnancy complications, including excessive foetal growth (both large for gestational age babies and those with excess body fat), risk of neonatal hyperinsulinemia, primary caesarean section and risk of pre-eclampsia. The independent associations of glucose with these outcomes persisted after adjustment for multiple potential confounders, including maternal Body Mass Index (BMI) [6, 8]. HAPO also considered the potential role of glycosylated haemoglobin (HbA1c) in the detection of GDM, but concluded that HbA1c was not sufficiently discriminatory to be of value in this setting. Further, HAPO confirmed the Pedersen hypothesis [9] by

clearly demonstrating the association between even mild degrees of maternal hyperglycaemia and the foetal consequences of LGA, increased adiposity and hyperinsulinemia.

Importantly, the HAPO study demonstrated no threshold for glucose associations with adverse outcomes, suggesting that new diagnostic criteria for GDM would need to be developed through a consensus process, a conclusion reached one and a half decades previously by Sacks et al. [10]. The consensus process auspiced by IADPSG subsequently developed a two stage protocol for diagnosis of GDM and related disorders, summarized in Fig. 28.2. The recommended diagnostic values for GDM were determined by consensus. They were based on the risks of foetal outcomes related to maternal glycaemia, specifically LGA, neonatal adiposity (body fat >90th centile) and neonatal hyperinsulinemia. The diagnostic glucose thresholds chosen (fasting, 1 h or 2 h at 75 g OGTT) were those associated in continuous statistical models with Odds Ratios of 1.75 compared to the HAPO cohort mean for the three outcomes mentioned above, after extensive adjustment for other confounders [7].



**Fig. 28.2** IADPSG recommended diagnostic pathway for overt diabetes in pregnancy and gestational diabetes

In recognition of the increasing prevalence of pre-pregnancy diabetes (principally Type 2 diabetes) and obesity in women of reproductive age across many populations, IADPSG recommended early pregnancy testing for undiagnosed, severe degrees of hyperglycaemia in early pregnancy. Implementation of early pregnancy testing on a universal or selective (risk factor based) basis was left open in the IADPSG recommendations due to the lack of firm data in this field and the widely varying diabetes prevalences in different populations around the world. The IADPSG Guidelines recommend that testing be undertaken using any of the following: fasting glucose, HbA1c or random glucose (with confirmation) and that the results should be assessed using existing non-pregnancy-specific diagnostic criteria (see Fig. 28.2).

Those women with results consistent with diabetes outside pregnancy should be labelled as

having “Overt Diabetes” in view of their more severe hyperglycaemia. Further, hyperglycaemia of this degree, if detected in early pregnancy, is likely to have antedated the diagnosis of pregnancy. Clinically, these women have been shown to have high rates of established microvascular diabetes complications [11] and thus demand urgent attention, both for their pregnancy care and for management of their diabetes and associated complications.

The IADPSG recommends that all women not previously identified as having abnormal glucose metabolism should undergo a formal 75 g OGTT at 24–28 weeks’ gestation. Non-fasting glucose challenge tests, favoured in some previous diagnostic algorithms, are not recommended due to limited sensitivity [12] and lack of clear associations with pregnancy outcomes. Following the IADPSG criteria, GDM is diagnosed if any one

of the three relevant glucose values (fasting, 1 or 2 h post 75 g glucose load) equal or exceed the thresholds noted in Fig. 28.1. If a fasting test is performed in early pregnancy, some women may be diagnosed as GDM at this stage. Otherwise, the diagnosis would generally be made at 24–28 weeks.

Given the fine distinctions to be drawn between normal and abnormal results, standardization and calibration of glucose measurements at the OGTT and at other testing points in pregnancy is critical. Venous plasma glucose should be used for all measures and laboratories should pay careful attention to methodology and quality control [7].

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### Differential Diagnosis/Other Considerations

Since GDM is most commonly an asymptomatic condition diagnosed on the basis of glucose concentrations during the exogenous stress of an OGTT, differential diagnosis is not generally an important clinical consideration. However, it is important to consider other aspects of the condition including [1] other specific forms of abnormal glucose metabolism which may present as GDM and [2] important maternal and pregnancy factors which predispose to GDM.

Monogenic causes of diabetes are increasingly recognized and though they tend to comprise only a small proportion of cases, they may be first detected in pregnancy due to increased glucose testing. Autosomal mutations causing diabetes are commonly grouped under the heading of Maturity Onset Diabetes of the Young (MODY). Collectively, MODY variants may account for up to 10 % of cases of GDM [13].

The example of glucokinase gene (GCK) mutations causing MODY2 [14] is particularly instructive. GCK mutations in the mother are associated with mild fasting hyperglycaemia, generally without other abnormalities on the oral glucose tolerance test. If the foetus carries the same mutation, birthweight tends to be normal as both mother and foetus are adapted to “sensing”

glucose at the same level. By contrast, if the mother carries the GCK mutation (and therefore is mildly hyperglycaemic) and the foetus is normal, birthweight is increased. Conversely, if the mother is normal and the foetus carries the GCK mutation, birthweight is reduced. This elegant experiment of nature demonstrates the potential importance of both genes and environment in determining foetal growth.

Autoimmune diabetes, including early Type 1 diabetes and Latent Autoimmune Diabetes of Adult Life (LADA) may also be detected due to glucose testing in pregnancy. The definitive diagnosis is not always clear in this instance. In a recent case series from France, this form of diabetes, described as “Type 1 diabetes masquerading as GDM” was associated with pregnancy complications [15]. Prevalence of GAD or islet cell antibodies has been reported to be as high as 6 % in some GDM cohorts [16] and is associated with a higher incidence of progression to overt diabetes post-partum.

The use of clinical risk factors for prediction of GDM is of limited utility and this forms one argument in favour of universal diagnostic testing in pregnancy. Increased placental size, as seen in multiple pregnancies, is associated with a higher risk of GDM in some studies [17]. Whilst a number of demographic and anthropometric factors, such as maternal age, ethnicity, body mass index and previous history of GDM or macrosomia are associated with higher risk of GDM, no one factor or combination of factors offers sufficient discriminatory power to obviate biochemical assessment.

Reported recurrence rates of GDM in subsequent pregnancies vary from 36 to 69 % [18]. Recurrence risk appears higher in the presence of maternal obesity, early diagnosis of GDM in the index pregnancy and excessive inter pregnancy weight gain. It remains unclear why recurrence rates for GDM are not higher than observed, given that women are by definition older and frequently heavier at the time of subsequent pregnancies. This observation does suggest that variability in the interaction between a woman and a particular foetus (or foeto placental unit) may play a role in the aetiology of GDM.

## Current and Future Therapies

Current therapy for GDM is largely “glucentric”, with the major therapeutic goal being achievement of glucose levels as close to normal pregnancy values as possible. Our discussion will include the current definition of normoglycaemia in pregnancy, evidence favouring treatment, available therapeutic modalities, recent evidence for the use of ultrasound estimation of foetal growth to guide the intensity of treatment and decisions regarding the mode and timing of delivery. Post-partum follow-up for the woman with GDM will also be addressed.

## Normoglycaemia in Pregnancy

The definition of normal pregnancy glucose levels, both fasting and in the postprandial state, has been investigated by a variety of methods, including detailed hospital inpatient studies, ambulatory studies using capillary glucose meters and continuous glucose monitoring (CGMS) over many years. A comprehensive analysis of this literature was published by Hernandez et al. in 2011 [19] and concluded that mean glucose levels in normal weight pregnant women were lower than previously described (Mean  $\pm$  SD Fasting  $71 \pm 8$  mg/dL or  $3.9 \pm 0.4$  mmol/L; 1 h post meal  $109 \pm 10$  mg/dL or  $6.1 \pm 0.6$  mmol/L; 2 h post meal  $99 \pm 10$  mg/dL or  $5.5 \pm 0.6$  mmol/L). The commonly used statistical upper limits of these observations (Mean + 2 SD) are also substantially lower than current, largely empirical, glucose treatment targets advocated in GDM [20–25] (Table 28.1) The determination of optimal glucose targets remains contentious, although the current recommendations of major professional bodies are largely congruent. The values mentioned in Table 28.1 are the maximal glucose values in the fasting and post-prandial states considered acceptable by the relevant organizations, or reported as treatment targets by the randomized controlled trials. The abbreviations and data sources for Table 28.1 are as follows: ADA—American Diabetes Association [20, 22]; ADIPS—Australasian Diabetes in Pregnancy

**Table 28.1** Glucose targets recommended by major national organizations in gestational diabetes or reported in major randomized controlled trials

Organization	Fasting ( $\leq$ )	1 h post meal ( $\leq$ )	2 h post meal ( $\leq$ )
ADA	95 mg/dL 5.3 mmol/L	140 mg/dL 7.8 mmol/L	120 mg/dL 6.7 mmol/L
ADIPS	99 mg/dL 5.5 mmol/L	144 mg/dL 8.0 mmol/L	126 mg/dL 7.0 mmol/L
ACOG	95 mg/dL 5.3 mmol/L	130 mg/dL 7.2 mmol/L	
NICE	106 mg/dL 5.9 mmol/L		140 mg/dL 7.8 mmol/L
DIPSI	90 mg/dL 5.0 mmol/L		120 mg/dL 6.7 mmol/L
CDA	95 mg/dL 5.3 mmol/L	140 mg/dL 7.8 mmol/L	120 mg/dL 6.7 mmol/L
Trial			
ACHOIS	99 mg/dL 5.5 mmol/L		126 mg/dL 7.0 mmol/L
MFMN	95 mg/dL 5.3 mmol/L		120 mg/dL 6.7 mmol/L

Society [21]; ACOG—American College of Obstetricians and Gynecologists [22]; NICE—National Institute of Clinical Excellence (UK) [22]; DIPSI—Diabetes in Pregnancy Society India [23]; CDA—Canadian Diabetes Association [24, 25]; ACHOIS—Australian Carbohydrate Intolerance Study [26]; MFMN—Maternal Foetal Medicine Networks study [27]

## Evidence for Treatment of GDM

Although the clinical importance of treating GDM was hotly debated for many years, two recent randomized controlled trials have now been conducted, with largely congruent results. The ACHOIS study [26], conducted principally in Australia, randomized 490 women to an intervention including dietary advice, home blood glucose monitoring and insulin therapy as required and compared them to 510 women assigned to standard care. The primary composite outcome of serious perinatal complications (death, shoulder dystocia, bone fracture or nerve palsy) was reduced from 4 to 1 % ( $p=0.01$ ) with intervention. Only 20 % of women required adjunctive insulin treatment. The rates of LGA and macrosomia (defined as birthweight  $\geq 4,000$  g)

were also reduced, with no increase in small for gestational age (SGA) babies. Quality of life was improved with treatment and hypertensive complications of pregnancy were less frequent. Treated women had higher rates of induction of labour, but similar rates of caesarean delivery. Admission of neonates to the neonatal nursery was more frequent with intervention, possibly related to hospital policies.

The USA based Maternal-Foetal Medicine Units Network trial of the treatment of mild GDM [27] randomly assigned 485 women to intervention vs. 473 assigned to standard care. This study excluded women with fasting glucose  $\geq 95$  mg/dL, but required them to have 2 / 3 other OGTT values in excess of ADA thresholds for the diagnosis of gestational diabetes [22]. The composite outcome used in this trial included both perinatal mortality and neonatal outcomes associated with maternal hyperglycaemia (hypoglycaemia, hyperbilirubinemia, hyperinsulinemia and birth trauma. Fully 92 % of treated women were managed by lifestyle interventions, with only 37/485 or 7.6 % needing adjunctive insulin therapy. As with the ACHOIS study, the rates of LGA and macrosomia were reduced with treatment as was neonatal fat mass. Hypertensive disorders of pregnancy, caesarean section, maternal weight gain from enrolment and shoulder dystocia were all reduced by active intervention. The composite neonatal outcome did not differ between the treatment groups.

Considering these two trials together, we conclude that active treatment of women with GDM reduces serious pregnancy complications including hypertensive disorders of pregnancy and excessive foetal growth and its consequences. Thus, after many years of debate, active treatment of GDM appears justified.

## Current Therapy of GDM

Lifestyle modification, including medical nutrition therapy and encouragement of physical activity, forms the primary mode of therapy for GDM. As noted above, such therapy proved sufficient in 80–90 % of women enrolled in the two major randomized trials. The American Dietetic Association

evidence based nutrition practice guidelines for GDM [28] provide a sound overall framework for nutritional interventions. They advocate review by a registered dietitian within 1 week of GDM diagnosis and a minimum of two follow up visits. Whilst dietary recommendations are individualized, the general guidance favours mild energy restriction to approximately 70 % of recommended daily intake for overweight/obese women and reduction of total carbohydrate intake to less than 45 % of total caloric intake. Other recent studies have specifically examined the role of glycaemic index in nutritional therapy for GDM [29] and have suggested that this may enhance the effects of standard treatment and assist some women in meeting glycaemic targets and obviating the need for pharmacotherapy, although overall pregnancy outcomes have been reported as similar to those achieved with a high-fibre diet [30].

Insulin therapy remains the cornerstone of treatment for women who fail to meet glycaemic goals after lifestyle modification. The glucose targets currently recommended by various international organizations and those used in the two major randomized trials are listed in Table 28.1. The precise insulin regimen used for an individual woman depends on the pattern of elevated glucose readings seen on home glucose monitoring. Women with predominant fasting hyperglycaemia may respond well to a single evening injection of intermediate or long-acting insulin. Those with predominant elevation of post-prandial glucose are generally treated with soluble insulin or a rapid-acting analogue insulin prior to meals. Women with a mixed pattern of elevated glucose readings may also be treated with premixed insulins, generally twice daily at breakfast and dinner time. A recent detailed review [31] has concluded that there is minimal evidence available to choose between specific insulin regimens.

## Newer Therapeutic Options

Oral hypoglycaemic agents, principally glibenclamide (glyburide in the USA) and metformin, have also been trialled in gestational diabetes. The first major randomized controlled trial of glyburide, conducted by Langer and colleagues

[32] reported equivalent glucose control and no substantial differences in outcomes in women treated with glyburide as compared to insulin after failure of lifestyle management. Langer's study was not powered to examine major pregnancy outcomes. Subsequently, a systematic review of this and subsequent randomized trials [33] reported no differences in terms of glycaemic control or pregnancy outcomes when comparing glyburide and insulin therapy. However a large recent (non-randomized) cohort report of 10,682 women from the "Sweet Success" programme in California reported increased rates of LGA and neonatal intensive care unit admission in those women treated with glyburide [34].

Metformin has also been evaluated in one large [35] and two smaller randomized trials [36, 37]. These studies included women who failed to meet glycaemic targets after lifestyle interventions for GDM. They demonstrated very similar glucose control and pregnancy outcomes with metformin therapy when compared to standard insulin treatment. The rate of supplemental insulin therapy was high overall—46 % in the MiG study and 32 % in the Finnish report but surprisingly no patients in the study from New Mexico USA required supplemental insulin therapy. Patient preferences were clearly in favour of metformin therapy.

Uncontrolled reports suggested that metformin reduces pregnancy complications in women with polycystic ovarian syndrome treated during pregnancy [38–40], but a recent randomized trial failed to confirm any benefit [41].

Two randomized trials [42, 43] comparing metformin with glyburide/glibenclamide in the treatment of GDM have shown somewhat discordant results. In a report from Brazil [42, 44] Silva et al. reported comparable efficacy between these two medications, with supplemental insulin required in around 25 % of each group. In contrast, Moore et al. [43] reported that 35 % of metformin treated women required supplemental insulin as compared to 16 % of those treated with glyburide.

The use of oral hypoglycaemic agents in the treatment of GDM varies widely on a country by country basis, with glyburide favoured in the USA [45], whilst metformin is recommended more widely in the United Kingdom and Australasia [46–48]. Some practitioners remain

concerned by the possibility of adverse foetal effects of oral drugs. Glyburide has been reported only at very low levels in cord blood, due to limited transplacental passage and active counter transport [49, 50]. Metformin crosses the placenta readily [51–53] but has shown no adverse foetal or early childhood effects to date [54, 55].

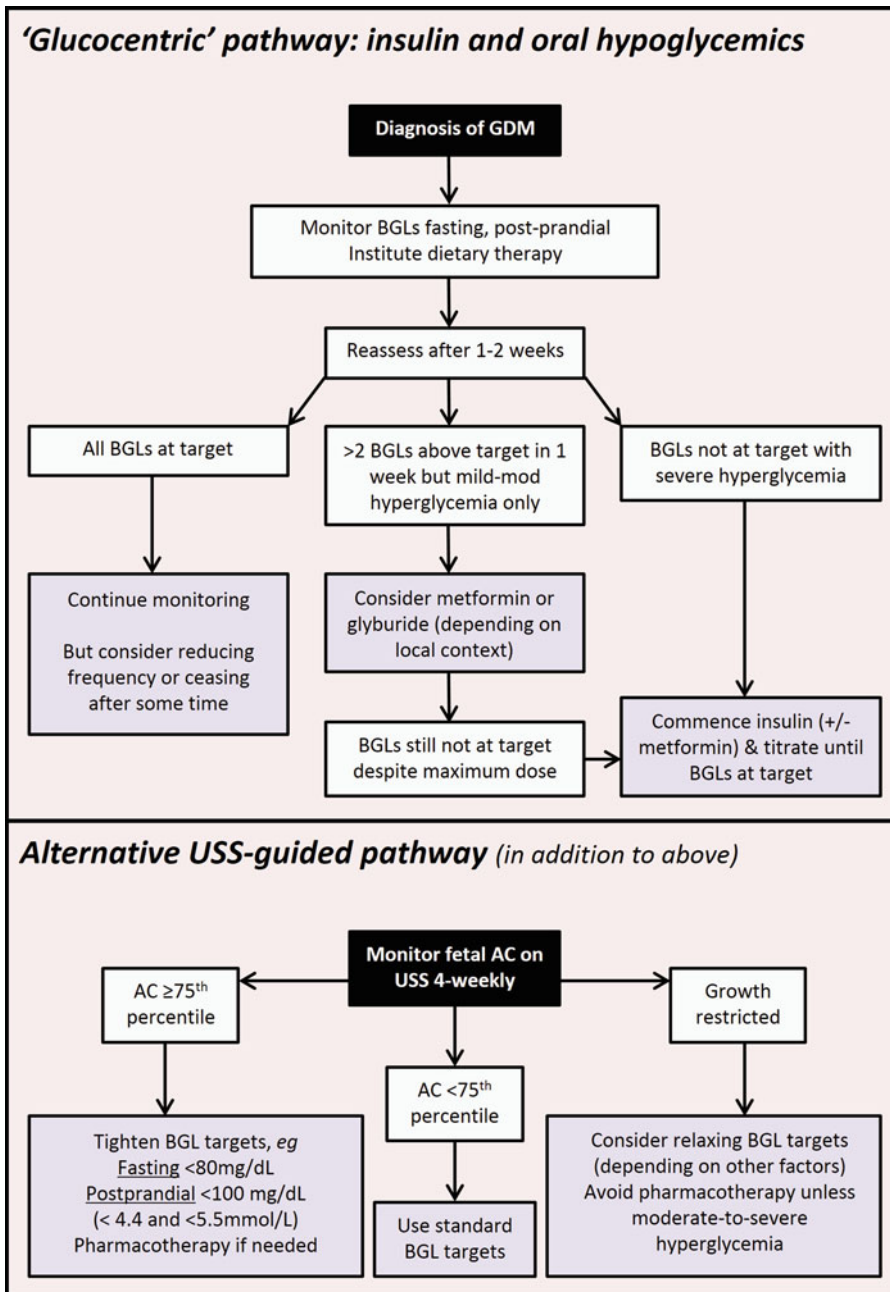
As noted above, many of the adverse effects of GDM relate to excessive foetal growth, driven by nutrient excess and consequent foetal hyperinsulinism as outlined in the Pederson hypothesis [9] and its subsequent modification by Freinkel and Metzger [5]. These have also been presented in Fig. 28.1. Direct assessment of amniotic fluid insulin concentrations, pioneered by Weiss et al. [56] demonstrated that foetal hyperinsulinemia was associated with increased risks of pregnancy complications. In turn, Schafer Graf et al. [57] noted that foetal abdominal circumference (AC) on ultrasound could be used to non-invasively predict foetal hyperinsulinism and identify those babies most at risk of diabetic fetopathy.

Subsequently, an alternative approach to treatment of GDM, based on ultrasound assessment of foetal growth, in particular foetal AC, has been proposed and evaluated in four randomized studies [58–62]. According to this approach, summarized by Kjos et al. [60], glucose lowering treatment may be intensified in those pregnancies where the foetus shows evidence of accelerated growth, generally determined by foetal AC > 75th centile for gestational age on ultrasonographic assessment. These protocols suggest that "low risk" pregnancies, as defined by normal (<75th centile) foetal AC, may require less stringent glycaemic control and conversely that detection of an increased AC should lead to intensification of glucose lowering therapy.

A summary of the traditional (glucocentric) and alternative (USS guided) pathways for GDM therapy is presented in Fig. 28.3.

### **Foetal Surveillance and Timing of Delivery**

Despite a lack of high-level evidence of definite benefit, foetal ultrasound is frequently used to assess foetal well being and to estimate foetal



**Fig. 28.3** Treatment pathways for GDM—“glucocentric” pathway including treatment with insulin and oral hypoglycemic agents and alternative “USS guided” pathway. For details see text

weight to assist in determining the timing and mode of delivery. Most units have extrapolated their practices in this area from those developed for pre-gestational or pre-existing diabetes.

The experience reported by the Diabetes Unit at the National Maternity Hospital Dublin in 1983

and again in 1992 is particularly instructive [63]. They noted that the only deaths in normally formed infants occurred when there was clinical evidence of foetal macrosomia, polyhydramnios or poor metabolic control. Consequently in their absence, this group of experienced clinicians



allowed the otherwise uncomplicated pregnancies to go to full term (40 completed weeks of gestation) [64]. This non-interventionist approach produced a caesarean section rate of 7 % and vaginal delivery was achieved in 90 % of women!

The widespread practice of cardiotocographic foetal monitoring in GDM in the absence of other obstetric indications such as foetal growth restriction and the hypertensive disorders is likewise poorly supported by evidence. The current protocols are largely empiric and driven by expert opinion. The report of Landon et al. [65], which considered women with Type 1 diabetes, noted that foetal surveillance most commonly led to intervention in women with associated vascular disease, such as hypertension or nephropathy.

Gabbe and colleagues recommended that in uncomplicated GDM pregnancies, CTG monitoring should be commenced after 40 weeks' gestation whilst awaiting spontaneous onset of labour [66]. However, there is again a paucity of high-level evidence in this area to guide the clinician.

A 2001 Cochrane review [67] found that there was only one randomized controlled trial [68] comparing planned elective delivery at 38 weeks' gestation vs. expectant management (awaiting the onset of spontaneous labour up to 42 weeks' gestation, with twice weekly CTG and amniotic fluid volume surveillance). This trial included a range of insulin treated women, rather than simply women with gestational diabetes. The review concluded that induction at 38 weeks did not result in an increase in caesarean section RR 0.81 (95 % CI 0.52–1.26). However, the risk of macrosomia (birthweight  $\geq 4,000$  g) was lessened in the elective delivery group RR 0.56 (95 % CI 0.32–0.98) and there were three cases of mild shoulder dystocia in the expectant group. The authors concluded that there was insufficient evidence to make a conclusive recommendation.

## Mode of Delivery

The major concern regarding vaginal delivery in women with gestational diabetes is the potential risk of shoulder dystocia and in particular resultant brachial plexus palsy. Ultimately, the relative size of the foetal shoulders and the maternal pelvis, the

strength of the uterine contractions and the mother's expulsive efforts and the foetal diameters determine the likelihood of successful vaginal delivery. None of these can be reliably measured and/or predicted.

Although increasing foetal weight is positively associated with an increasing risk of shoulder dystocia, as many cases occur in babies with birthweight less than 4,000 g as those who are classified as being macrosomic (i.e. birthweight  $> 4,000$  g). Furthermore 50 % of cases of brachial plexus palsy occur in the absence of shoulder dystocia, suggesting that ante and intrapartum factors also play an important aetiological role in its genesis [69].

Despite overall uncertainties, it is common practice to offer elective caesarean delivery if the estimated foetal weight is 4,000 or 4,250 g or more [70].

## Postpartum Follow Up

The diagnosis of GDM carries long term health implications for both mother and baby. In particular, the risk of future diabetes for the mother is substantial and the diagnosis of GDM offers an opportunity for diabetes prevention. Whilst the foetal/neonatal effects for GDM are important, we consider them to be outside the scope of the current discussion.

Women with GDM should be encouraged to breast feed. In addition to benefits for their offspring [71], there is evidence that this may reduce their own risk of progression to diabetes [72, 73].

In the immediate postnatal period, maternal glycaemia returns to normal in most cases. However, women first detected as having "Overt diabetes" in early pregnancy clearly require close monitoring as they are likely to have ongoing hyperglycaemia. For many of these women, the clinical diagnosis of diabetes will be obvious, though in borderline cases repeat testing may improve diagnostic clarity.

For the majority of women with GDM, glucose status should be re assessed at 6–8 weeks post-partum, generally with a repeat 75 g OGTT [21, 74]. Those women identified as having overt diabetes at this time clearly require immediate

care. Those with milder persisting abnormalities in glucose metabolism (IGT or IFG) at this time require annual follow up and may benefit from interventions designed to prevent progression to diabetes. Women with normal OGTT results at this stage should be tested every 2 years whilst in the reproductive age range and ideally pre-pregnancy for any further planned gestations [21, 74].

The absolute risk of a woman with GDM progressing to overt diabetes over time varies substantially between populations, with Kim et al. noting cumulative incidence rates of Type 2 DM varying from 2.6 to 70 % in various studies [75], with fasting glucose at the time of the diagnostic OGTT a major determinant. More recently, a meta-analysis by Bellamy et al. [76] has shown a relative risk of around ten for progression to Type 2 diabetes following GDM (compared to non-GDM women) across a broad range of studies. Thus, identification of these women at the time of pregnancy offers a unique opportunity for future diabetes prevention [77].

## Summary and Conclusions

The importance of gestational diabetes in obstetric practice has evolved rapidly with the global increase in maternal obesity and age at delivery. New diagnostic criteria have been developed and potentially important underlying etiologies such as monogenic and autoimmune diabetes have been identified in particular populations.

Whilst universal acceptance of the new diagnostic strategies has yet to be achieved, widespread recognition of the value of a uniform approach to diagnosis and classification of hyperglycaemia in pregnancy is evolving. Ongoing points of contention in treatment of GDM include the potential role of oral hypoglycaemic agents and the use of “customized” glycaemic treatment targets adjusted according to assessments of foetal growth.

Many aspects of therapy of GDM remain steeped in tradition, but high-level evidence is slowly accumulating to guide future practice. Evidence in the area of optimal foetal surveil-

lance, timing and mode of delivery remains sparse, with clinical decisions based more on local preferences and protocols than on high-level evidence.

A diagnosis of GDM identifies a pregnant woman as being at risk of future diabetes and offers the opportunity for prevention of this potentially devastating disease. It may also serve to identify “at-risk” families and offer broader opportunities for prevention of obesity and Type 2 diabetes in her offspring.

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## Present and Future Therapies

Insulin resistance in the liver and muscle, as well as  $\beta$  cell failure in the pancreas, are the traditional pathophysiologic defects of type 2 diabetes. Metformin, which acts primarily in the liver; thiazolidinediones, which primarily act in the muscle; and sulfonylureas, which increase  $\beta$  cell secretion of insulin, are examples of drugs that are used to correct or minimize these defects. Incretin deficiency and/or resistance, which can be treated by DPP-4 inhibitors, are also observed in diabetes. DPP-4 inhibitors improve  $\alpha$  cell function and decrease hyperglucagonemia, which contributes to hyperglycemia. Fast-action bromocriptine is available to treat insulin resistance in the brain [3].  $\alpha$ -glucosidase inhibitors decrease the intestinal absorption of glucose [4], whereas reabsorption of glucose in the kidney can be inhibited by SGLT2 inhibitors, which is currently under investigation [5].

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## Metformin

Metformin is a biguanide drug. Because insulin resistance is considered the main defect in type 2 diabetes, metformin is considered a first-line drug in the management of hyperglycemia [6, 7]. If there is no contraindication to metformin, it is considered by several guidelines to be a first-line treatment option immediately after diagnosis [6, 8]. *History.* Metformin was first synthesized in the 1920s, but, due to the discovery and availability of insulin at the same time, it was not studied in clinical trials until the 1950s, when the first trial was published [8]. Together with phenformin, metformin was introduced in clinical practice in 1957 [9]. Phenformin was later withdrawn from the market due to an association with lactic acidosis. Although there was an initial delay in the approval of metformin in the USA (1995), it is currently the most prescribed antidiabetic drug in the United States and around the world. *Mechanism of action.* Metformin acts by different mechanisms and can be used to both prevent and to treat diabetes. Its main target is the liver, where it decreases basal hepatic glucose output, activates AMPK (AMP-activated protein kinase) and inhibits gluconeogenesis [8, 9]. Its action in the skeletal muscle is not as significant. There are some observational data that suggest that metformin may protect against cancer [10]. *Pharmacokinetics.* Metformin is absorbed in the small intestine and reaches its maximal concentration ( $C_{max}$ ) 1–2 h after ingestion, with a half-life ranging between 1.5 and 4.9 h. Unlike

sulfonylureas, metformin is not bounded to plasma proteins [9]. It is eliminated primarily (90 %) by the kidney via glomerular filtration or tubular secretion. *Administration.* Metformin should initially be administered in small doses (500 or 850 mg after the largest meal of the day) to minimize the occurrence of gastrointestinal adverse effects. Afterwards, the dose should be increased, with increments of one tablet every week until the maximal dose of 2,550 mg/day is achieved. The extended-release formulation is generally administered once per day during the evening meal and also requires titration. Metformin is also available in combination with glipizide, glyburide, pioglitazone, repaglinide, and sitagliptin. *Efficacy.* Metformin decreases HbA<sub>1c</sub> by 1.5 % and fasting glycemia by approximately 20 % [11]. The typical effective dose is 1,500–2,000 mg/day. *Adverse effects.* Nausea, vomiting, flatulence, anorexia, and diarrhea are the most frequent adverse effects observed with metformin. These effects can generally be avoided if the dose is adequately titrated, as described above. Approximately 3 % of patients experience a metallic taste; this effect usually resolves spontaneously. Lactic acidosis can occur because metformin blocks gluconeogenesis, resulting in the accumulation of lactate. However, this complication is very rare (1 case/100,000 person-years of exposure), as long as the drug is not administered to those with contraindications. Lactic acidosis is an extremely serious condition with a mortality rate of up to 50 %. Symptoms, such as nausea, vomiting, abdominal pain, anorexia and/or hypotension, are generally non-specific. Metformin reduces intestinal absorption of vitamin B<sub>12</sub>, and inadequate levels of this vitamin have been shown to occur in less than 10 % of patients [12]. This deficiency rarely causes megaloblastic anemia and usually reverses after discontinuation of metformin. Measurements of serum vitamin B<sub>12</sub> every 2–3 years may be useful to prevent complications due to B<sub>12</sub> deficiency. *Contraindications.* Any condition in which the risk of acidosis is increased contraindicates the use of metformin. These conditions include congestive heart failure class 3 or 4, renal disease (men with serum creatinine  $\geq 1.5$  mg/dl or women

$\geq 1.4$  mg/dl), impaired hepatic function, acute myocardial infarction, septicemia, cardiovascular collapse, and age  $>80$  years (unless creatinine clearance is adequate). If the patient requires any radiological studies with iodinated contrast, metformin should be discontinued temporarily 48 h before and after the procedure because the contrast agent can cause renal dysfunction. Metformin should also be discontinued for any major surgery. *Advantages and disadvantages.* Metformin does not cause weight gain and can cause weight loss. It acts directly on the main defect of type 2 diabetes (insulin resistance) and also affects lipid metabolism, decreasing triglycerides, and LDL. It can be used in combination with many other oral drugs, as well as with insulin. It is considered a nonexpensive drug. The only disadvantage is the possibility of adverse events, mainly gastrointestinal side effects.

## Sulfonylureas

Despite some disadvantages, sulfonylureas have been used to manage type 2 diabetes for more than 50 years and, together with metformin, are the most widely used class of drugs for the treatment of type 2 diabetes. There are six sulfonylureas currently available in the USA: first-generation chlorpropamide, tolbutamide, and tolazamide and second-generation glyburide (glibenclamide), glipizide, and glimepiride. *Mechanism of action.* Sulfonylureas target the receptor SUR, which is found on the surface of  $\beta$ -cells. This receptor is one of two subunits in the ATP-dependent potassium channel (the other subunit is the channel itself). After binding to the SUR receptor, sulfonylureas cause the ATP-dependent potassium channel to close, resulting in an accumulation of potassium inside the  $\beta$ -cell and a subsequent influx of calcium, ultimately leading to depolarization of the cell. Higher concentrations of intracellular calcium stimulate the migration of insulin granules to the cell surface, where they fuse to the membrane and release insulin into the bloodstream. Sulfonylureas do not seem to have a direct effect on the liver, peripheral tissues, or muscle. Instead, the effects on these

tissues are realized via increased insulin secretion. *Pharmacokinetics.* After oral administration, sulfonylureas are almost completely absorbed and metabolized by the liver. First-generation sulfonylureas are extensively protein bound and excreted exclusively by the kidney. Second-generation sulfonylureas do not bind to circulating proteins and are excreted in different proportions in the urine and feces (glipizide 80 % urine and 20 % feces; glyburide 50 % urine and 50 % feces; glimepiride 60 % urine and 40 % feces). The onset and duration of action differ among the different drugs. All sulfonylurea agents except chlorpropamide have a short plasma half-life (4–10 h). The half-life of chlorpropamide is longer than 24 h. *Administration.* Usually sulfonylureas are not prescribed first line. Instead, they are commonly used after metformin. This combination can decrease the possibility of weight gain. Thiazolidinediones,  $\alpha$ -glucosidase inhibitors, and insulin can also be given in combination with sulfonylureas. Due to the risk of hypoglycemia, patients should be started on a low dose of sulfonylurea, which should be increased gradually every seven days depending on the level of glycemia. If the patient adheres to his/her diet and/or loses weight, it is likely that the dose can be decreased. Chlorpropamide is administered once daily due to its longer half-life, whereas tolbutamide is administered two to three times a day, due to its very short half-life. Second-generation drugs can usually be given once a day, but maximal doses must sometimes be given in two daily doses. *Efficacy.* Sulfonylureas can decrease HbA1c by 1–2 %. Like other antidiabetic drugs, the poorer the glycemic control the greater the improvement. Glimepiride and glyburide have the highest affinity for the SUR receptor and are the most potent sulfonylureas. Tolbutamide seems to be the least potent. The best candidate to receive a prescription of a sulfonylurea is a patient who is insulin deficient with sufficient residual  $\beta$ -cell secretion capacity. UKPDS as well as other studies have shown that the response to sulfonylureas diminishes over time, most likely because of the progressive decline in  $\beta$ -cell function. Monitoring glycemia and HbA1c are important to change treatment as soon as needed to avoid clinical in-

tia and the deterioration of diabetes control. Weight gain, poor compliance, a sedentary lifestyle, intercurrent illness (surgery, infection, and trauma), and inadequate dosage can also interfere in the efficacy. *Adverse effects.* Hypoglycemia is the most serious adverse event of sulfonylureas, and doctors and patients have to be aware of and watchful for this possibility [13]. Age, concomitant use of some drugs ( $\beta$ -blockers, coumarins, chloramphenicol, probenecid, inhibitors of MAO), impaired liver or kidney function, alcohol use, combined use with insulin, and prolonged exercise are risk factors for hypoglycemia. The risk of hypoglycemia is higher with glyburide than with glimepiride or gliclazide [14]. Weight gain can occur, as well as headache, asthenia, dizziness, and nausea. Hematological complications (hemolytic anemia, agranulocytosis, and thrombocytopenia) are rare and less likely to occur with second-generation sulfonylureas. Chlorpropamide can lead to hyponatremia due to water retention. Tolbutamide and chlorpropamide can cause flush if the patient drinks alcohol. Because ATP-dependent potassium channels are also present in cardiac cells and coronary vessels, sulfonylureas may decrease vasodilatation during myocardial infarction and cause more severe myocardial damage [15]. Gliclazide is more selective for pancreatic receptors and seems to have less cardiac adverse effects [15, 16]. *Contraindications.* Sulfonylureas cannot be used during pregnancy, and there are no studies establishing safety and effectiveness in pediatric patients. Because sulfonylureas are metabolized in the liver, they should be avoided in patients with hepatic dysfunction. Kidney dysfunction is also a relative contraindication, mainly to first-generation drugs that are excreted in the urine. *Advantages and disadvantages.* Understanding the mechanism of sulfonylureas can also shed light on sulfonylureas as a secretagogue class. On the one hand, sulfonylureas increase insulin secretion and decrease glycemia. On the other hand, long-term use could increase the possibility of  $\beta$ -cell failure. Furthermore, the increase in insulin secretion is independent of the level of glycemia, raises the risk for hypoglycemia. Another disadvantage of this class is the possibility of weight gain.



## Thiazolidinediones (TZD)

Thiazolidinediones activate peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) and improve insulin resistance, primarily in muscle [17, 18]. PPAR- $\gamma$  is a nuclear receptor that triggers various downstream effects. While the three drugs in this class have common effects, they also have unique effects [19]. Troglitazone (Rezulin), the first PPAR- $\gamma$  agonist, is no longer available due to concerns with hepatotoxicity. Rosiglitazone (Avandia) and pioglitazone (Actos) are currently on the market, but adverse cardiovascular outcomes have been observed with rosiglitazone [20, 21]. Pioglitazone, on the other hand, has a better activity on lipid metabolism, and the Proactive study [22] showed some cardiovascular benefits with this drug [17, 23, 24]. *Mechanism of action.* Classically, TZDs are insulin sensitizers that primarily act on muscle insulin resistance, in contrast to metformin, which primarily acts on the liver. Activation of PPAR- $\gamma$  by TZDs can stimulate expression of several genes, including those responsible for production of glucose transporters (GLUT). These changes improve insulin activity. Decreases in TNF- $\alpha$  and hepatic glucokinase help to lower hyperglycemia. TZDs can also modulate lipid metabolism and adipocyte differentiation. Different affinities for PPAR- $\alpha$  and PPAR- $\delta$  can explain the different clinical effects of the TZDs [23]. *Pharmacokinetics.* The main structure (thiazolidine-2-4-dione) of TZDs is common to all drugs in this class, and modifications in the side chain are responsible for differences in pharmacokinetics. TZDs are extensively bound to serum protein (>99 %). Cytochrome P450 enzymes are important for the metabolism of rosiglitazone (CYP2C8 and CYP2C9) and pioglitazone (CYP3A4). *Administration.* TZDs can be taken without regard to meals. They can be prescribed as monotherapy or in combination with metformin, DPP-IV inhibitors, sulfonylureas, or insulin [25]. Rosiglitazone is available in 2, 4, and 8 mg tablets to be given once or twice a day. There are 15, 30, and 45 mg tablets of pioglitazone and should always be taken once daily. Although no studies have demonstrated alterations in liver function tests, as was observed with troglitazone, it is recommended to measure liver function prior to initi-

ating therapy and periodically thereafter. Dose adjustments are not needed in patients with kidney dysfunction, but if there is any active liver disease or if serum ALT levels are >2.5 times the upper limit of normal, TZDs should not be prescribed. *Efficacy.* TZDs can decrease HbA1c by between 0.5 and 1.5 %. This decrease is similar for both pioglitazone and rosiglitazone [24, 26]. Because pioglitazone has a higher affinity for PPAR- $\alpha$ , it has a better lipid profile and has been shown to lower triglyceridemia and increase HDL [23, 24]. *Adverse effects.* Weight gain (1–4 kg) can occur due to changes in adipocyte differentiation. Metabolically, this increase in weight is not a large problem, because it generally correlates with a decrease in visceral fat and an increase in subcutaneous fat and a reduction in the number of large adipocytes and an increase in the small adipocytes, which results in lowering free fatty acids and reducing insulin resistance. The activation of PPAR- $\gamma$  can increase adipocyte formation rather than osteoblasts, which can increase the risk of osteoporosis and fractures [20]. Hypoglycemia is not a concern with TZDs, but may be in patients taking a TZD with a sulfonylurea or a TZD and insulin. Due to volume expansion, edema, anemia, and heart failure can occur [21]. Edema generally occurs if TZDs are combined with insulin. There are some data suggesting that pioglitazone may increase the risk of bladder cancer [23]. *Contraindications.* TZDs can exacerbate heart failure and should be avoided in patients with NYHA class III or IV. *Advantages and disadvantages.* TZDs are good options for the treatment of type 2 diabetes. They are generally not used as monotherapy but can add benefits if prescribed in combination with others drugs. Anemia, heart failure, and osteoporosis, as well as controversy regarding cardiovascular risk are some limitations of this class. Pioglitazone is a good choice for patients who need to improve their lipid profile (triglycerides and HDL) [27].

## DPP-4 Inhibitors

In the last few years, a better understanding of the effects of incretin has identified new targets for diabetes treatment [28]. Glucose-dependent insuli-

notropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are incretins produced by intestinal K and L cells. Their activity in islets cells depends on glycemia. During hyperglycemia, they can stimulate  $\beta$ -cell and inhibit  $\alpha$ -cell function, thus increasing insulin and decreasing glucagon, resulting in normal glycemia. During hypoglycemia, insulin secretion decreases and glucagon increases to restore normoglycemia. The major problem to using GIP and GLP-1 in the treatment of diabetes is the fact that they are degraded by the DPP-4 enzyme and, consequently, have very short half-lives. GLP-1 agonists/analogs with longer half-lives or DPP-4 inhibitors can be used as clinical tools [28]. Sitagliptin, linagliptin, alogliptin and saxagliptin are DPP-4 inhibitors available in the United States. Vildagliptin is available in other countries around the world. *Mechanism of action.* Oral intake of glucose can induce a higher increase in insulin secretion than venous glucose administration. This is called the incretin effect and is mediated by intestinal hormones, mainly GIP and GLP-1. Gliptins act by inhibiting the enzymatic breakdown of GIP and GLP-1, thereby prolonging their effects in several tissues. *Pharmacokinetics.* Gliptins are quickly absorbed after oral administration. Sitagliptin is metabolized in the liver by CYP3A4, and 79 % is excreted unchanged in the urine. Patients with kidney failure need dosage adjustments of saxagliptin, sitagliptin, alogliptin, and vildagliptin. There is no clinically relevant interaction with other drugs. *Administration.* Oral administration with or without food is recommended (saxagliptin (2.5 or 5.0 mg/day), linagliptin (5 mg/day), alogliptin (6.25, 12.5, or 25 mg/day) and sitagliptin, except if given in combination with metformin, when the dose is divided and taken twice daily. Vildagliptin 50 mg is given twice daily. In patients with kidney failure, dosage adjustments must be made for saxagliptin (2.5 mg/day if GFR <50 mL/min/1.73 m<sup>2</sup>), sitagliptin (50 mg if GFR 30–50 mL/min/1.73 m<sup>2</sup> and 25 mg if <30 mL/min/1.73 m<sup>2</sup>) alogliptin and vildagliptin. *Efficacy.* These drugs cause a modest decrease in HbA1c (0.4–0.9 %) [29], and all the DPP-4 inhibitors appear to have similar efficacy [30]. The decrease in postprandial glycemia is more prominent than in fasting glycemia. For this reason, combination of DPP-4 inhibitors with metformin

is a good option because metformin decreases nocturnal hepatic glucose output, whereas gliptin decreases postprandial increments. The unique mechanism of action, which does not promote hypoglycemia, weight gain, or serious adverse effects [29], and the possibility (not yet proven in humans) of  $\beta$ -cell proliferation or protection make this class quite useful. *Adverse effects.* Patients taking gliptin usually do not complain about side effects [28]. DPP-4 is not specific for GLP-1, and, while the effects of DPP-4 inhibition on other DPP-4 substrates are unknown, they do not seem to be clinically relevant. Effects on immune function remain a concern; in clinical trials, nasopharyngitis, upper respiratory tract infection, and headaches occurred more often in patients treated with DPP-4 inhibitors [31]. When administered as monotherapy, the incidence of hypoglycemia with DPP-4 inhibitors was similar to that of placebo, but if administered in combination with a sulfonylurea, it is important to remember that sulfonylureas have a higher probability to cause hypoglycemia. If DPP-4 inhibitors are combined with metformin or pioglitazone, there is no additional risk of hypoglycemia. Cases of acute pancreatitis have been reported in patients on sitagliptin [32] as well as in patients treated with exenatide, but upon reviewing these cases the incidence is similar to that in the diabetic control group [33]. *Advantages and disadvantages.* The major advantage of the DPP-4 inhibitors is achieving good glycemic control without hypoglycemia. Effects beyond glycemia are still being studied and need to be confirmed. Preservation of  $\beta$ -cell function is also a possible advantage. The small decrease in HbA1c and the high cost are disadvantages. DPP-4 inhibitors are commonly used in combination with metformin and most of the other types of antidiabetic drugs, but if there is intolerance or any contraindication to metformin, pioglitazone, or sulfonylureas, the gliptins can be used as monotherapy.

### **$\alpha$ -Glucosidase Inhibitors**

Some studies have suggested that post-prandial glycemia (PPG) is a better predictor of cardiovascular risk than fasting glycemia [34]. In this context, the  $\alpha$ -glucosidase inhibitors offer the

possibility to decrease PPG while decreasing cardiovascular risk. This class was first available to reduce PPG, but due to the adverse gastrointestinal effects and the availability of DPP-4 inhibitors it is not commonly used. These drugs are a third-line choice for treating diabetes. There are two medications available: acarbose (Precose) and miglitol (Glyset). *Mechanism of action.*  $\alpha$ -glucosidase inhibitors reversibly bind to  $\alpha$ -glucosidases (sucrase, maltase, glucoamylase, isomaltase) found in the brush border and delay the absorption of carbohydrates in the small intestine, decreasing the PPG peak [4]. These enzymes assist in the digestion of oligosaccharides and disaccharides into monosaccharides. *Pharmacokinetics.* Acarbose only acts in the small intestine and is not absorbed, while miglitol is almost entirely absorbed and could have some additional extraintestinal effects, decreasing hepatic glycogenolysis (*in vitro studies*). Approximately 1–2 % of active acarbose is absorbed and, after metabolism in the liver, it is excreted by the kidneys. The bioavailability of miglitol ranges from 50 to 100 %, and absorption does not affect the hypoglycemic effectiveness. Miglitol is not metabolized and is excreted unchanged by the kidneys or, if not absorbed, in the feces. *Administration.* These drugs must be given with each meal, and, because of the gastrointestinal side effects, patients should gradually increase the dose to maximize effectiveness and decrease side effects. For example, patients can start with 25 mg tid and slowly increase the dose to 50–100 mg tid. Some patients will need to begin with a once-daily dose. Because the drugs only work in the presence of dietary carbohydrate, the doses should be given with the first bite of each meal. Acarbose is approved as monotherapy or in combination with metformin, sulfonylureas, or insulin. Miglitol is approved as monotherapy or in combination with sulfonylureas. *Efficacy.* There is a modest decrease in HbA1c (0.5 a 1.0 %) with these drugs [4]. The improvement in PPG (40–50 mg/dl) is better than the improvement in fasting glycemia (25–30 mg/dl). There is no head-to-head comparative study of the two  $\alpha$ -glucosidase inhibitors, but the efficacies of acarbose and miglitol seem to be similar. *Adverse effects.* Side effects are mainly gastrointestinal

and depend on the correct administration and titration of the dose. Because these drugs delay the absorption of carbohydrates, production of gas by the natural flora of the large intestine can lead to flatulence, abdominal distention, and diarrhea [35]. These side effects are usually transient but can occur in up to 60% of patients and are one limitation to the use of this class. During clinical trials, elevation in liver enzymes occurred in patients taking doses of 200–300 mg tid of acarbose, and the manufacturer recommends measuring liver function every 3 months during the first year [36]. The  $\alpha$ -glucosidase inhibitors do not cause hypoglycemia, but can do so if used in combination with sulfonylureas or insulin. If a patient taking combination therapy experiences an episode of hypoglycemia, he needs to use glucose tablets or a glucagon injection instead of food because complex carbohydrate absorption will be blocked. Neither acarbose nor miglitol cause weight loss. *Contraindications.* Because miglitol is eliminated by the kidney, it should not be used if creatinine clearance is lower than 25 ml/min/1.73 m<sup>2</sup> or if plasma creatinine is higher than 2.0 mg/dl. Both acarbose and miglitol are contraindicated in pregnancy and nursing as well as in diabetic ketoacidosis, inflammatory bowel disease, intestinal obstruction, colonic ulceration, and hypersensitivity to acarbose or miglitol.

## Glinides

The only glinides currently available are nateglinide and repaglinide. Glinides are secretagogue agents such as sulfonylureas, but they have a reduced risk of hypoglycemia due to their short half-life and can be taken only when the patient eats. *Mechanism of action.* Like sulfonylureas, glinides bind to a membrane receptor found in  $\beta$ -cells and close the ATP-dependent potassium channel, resulting in depolarization of the cell and opening of calcium channels [37]. The influx of calcium induces insulin secretion. Although their mechanism is very similar to that of sulfonylureas, the onset is faster and the duration is shorter (fast on, fast off). *Pharmacokinetics.* Inactive metabolites of repaglinide are excreted in the feces after metabolization via oxidative biotransformation.

Nateglinide is metabolized in the liver by CYP3A4 (30 %) and CYP2C9 (70 %), and approximately 16 % is excreted unchanged by the kidneys. *Administration.* Repaglinide is available in tablets of 0.5, 1, and 2 mg, and nateglinide is available in 60 and 120 mg tablets. Administration with food does not affect the bioavailability of repaglinide, but decreases that of nateglinide. Repaglinide can be taken at the start of each meal or 15–30 min before, while nateglinide is better taken 1–30 min before each meal [38]. If a meal is skipped or added, a dose of repaglinide must be skipped or added. *Efficacy.* Glinides act mainly on postprandial glycemia, and reduction of HbA1c is between 0.7 and 1.5 % [39]. Glinides can be used with other antidiabetic drugs, except for sulfonylureas. Because the efficacy and action are similar to that of sulfonylureas, if a patient is already on sulfonylureas, there is no advantage to change to glinides. *Adverse effects.* Like sulfonylureas, hypoglycemia can occur, but is less frequent. Weight gain can occur because glinides increase insulin secretion. Other adverse effects such as headache, arthralgia, nausea, upper respiratory infections, and constipation are rare. *Contraindications.* Glinides cannot be used during pregnancy or by nursing mothers. There are no studies in children, and the use of glinides in this population is not recommended. *Advantages and disadvantages.* Because of the lower incidence of hypoglycemia, older patients can experience some benefits with the glinides. The efficacy and action are similar to sulfonylureas, but because there is no sulfa moiety, patients with allergies to sulfa can use these drugs. Administration immediately prior to each meal is also an advantage for patients who do not eat at regular times throughout the day. Higher cost and lower HbA1c reduction than sulfonylureas are some disadvantages. No dose adjustment is necessary in patients with moderate renal failure. Nateglinide can also be used without adjustment in patients with moderate hepatic failure, but the dose of repaglinide may need to be reduced.

## Bromocriptine

Bromocriptine mesylate quick-release was approved by FDA in May 2009 and is the only antidiabetic drug that acts not in the pancreas,

liver, or muscle, but in the hypothalamus. *Mechanism of action.* Bromocriptine is an ergot derivate sympatholytic D2-dopamine agonist that acts centrally to modulate glucose and energy pathways, resulting in an increase in hypothalamic dopamine and inhibition of sympathetic and serotonergic activities. As a result, hepatic glucose output, insulin resistance, free fat acids, triglyceridemia, and glycemia are reduced. *Pharmacokinetics.* After oral administration, 65–95 % of an administered dose is absorbed, but only 7 % reaches the systemic circulation after first-pass hepatic metabolism. Bromocriptine is metabolized by CYP3A4 and excreted primarily in the bile, with only 2–6 % excreted in the urine. *Administration.* The quick-release bromocriptine is administered once daily, 2 h after waking, in the morning, with food to reduce the possibility of nausea. Patients generally start with one tablet (0.8 mg) and increase the dose by one tablet/week as needed, until the maximal dose of six tablets (4.8 mg) is reached. *Efficacy.* Bromocriptine reduces HbA1c by 0.4–0.8 % and can be used alone or in combination with any other antidiabetic drug [40]. *Adverse effects.* Nausea is the most common adverse effect (32 %) and can be reduced with dose titration. Asthenia, constipation, dizziness, and rhinitis can occur [40]. *Contraindications.* There are no studies in patients with renal or hepatic failure. Bromocriptine quick-release is different from the 2.5–5.0 mg bromocriptine that is used for pituitary adenomas. Psychosis, type 1 diabetes, and syncopal attacks are contraindications. *Advantages and disadvantages.* The mechanism of action is different from all other drugs used to type 2 diabetes. Therefore, bromocriptine can be an option for patients already on other drugs who are not able to achieve glycemic control. Bromocriptine can also reduce weight and a study has shown that it may also reduce cardiovascular events [3]. Adverse effects, mainly nausea, can limit its use.

## SGLT2 inhibitors

This is a new class of drugs to treat diabetes that act in the kidney. SGLT2 is a protein with 672 amino acids located in the proximal tubules. It has low

affinity but high capacity for reabsorbing glucose by a sodium dependent mechanism and against a concentration gradient. The inhibition of SGT2 decreases glucose reabsorption and increases urinary glucose excretion, improving glucose control in the diabetic patient. Canagliflozin (Invokana) is the first component of this class of drugs approved for treatment of type 2 diabetes. Administration: 100 mg once daily, before the first meal. Contraindications: renal impairment (eGRF

< 30ml/min/1.73m<sup>2</sup>). Side effects: female genital mycotic infections, urinary tract infections. Efficacy: decrease HbA1c around 0.9% [41].

## Conclusion

Some years ago we did not have so many drugs to treat diabetic patients. Currently, we have several options (Table 29.1). A thorough understanding

**Table 29.1** Oral drugs to treat type 2 diabetes.

Drug	Daily dose	Reduction in HbA1c	Side effects	Contraindications
Metformin (500, 850, 1,000 mg. Extended-release: 500/750 mg, 1,000 mg)	Initial small dose and titrate. Max 2,550 mg/day	1–2 %	Nausea, vomiting, flatulence, anorexia, abdominal pain, diarrhea	congestive heart failure (class 3 or 4), serum creatinine $\geq 1.5$ mg/dl (man) $\geq 1.4$ mg/dl (woman), impaired hepatic function, acute myocardial infarction, septicemia
Chlorpromamida (Diabinese) 100, 250 mg	Initial: 250 mg. Max: 750 mg	1–2 %	Hypoglycemia, weight gain, photosensitivity	Type 1 diabetes; pregnancy and nursing
Glimepiride (Amaryl) 1, 2, 4 mg	Initial: 1–2 mg. Max: 8 mg			
Glyburide (Diabeta) 1.25, 2.5, 5 mg	Initial: 2.5–5 mg. Max: 20 mg			
Glipizide 5, 10 mg. Extended-release 2.5, 5, 10 mg	Initial: 5 mg. Max: 20 mg			
Pioglitazone (Actos) 15, 30, 45 mg	Initial: 15–30 mg. Max: 45 mg	0.5–1.5 %	Weight gain, osteoporosis/fracture, bladder cancer (pioglitazone), cardiovascular event (rosiglitazone)	Heart failure NYHA class III and IV
Rosiglitazone (Avandia) 2, 4, 8 mg	Initial: 2 mg bid or 4 mg qd. Max: 8 mg			
Acarbose (Precose) 25, 50, 100 mg	Initial: 25 mg tid. Max: >60 kg–100 mg tid; <60 kg–50 mg tid	0.4–1.0 %	flatulence, abdominal distention, diarrhea. If in combination with other drug and patient develop mild hypoglycemia, use dextrose, not sucrose (cane sugar) to treat.	Renal failure (Clearance Cr < 25 ml/min or creatinine > 2 mg/dl. Ketoacidosis, bowel disease, colonic ulceration
Miglitol (Glyset) 25, 50, 100 mg	Initial: 25 mg tid. Max: 100 mg tid			
Nateglinide (Starlix) 60, 120 mg	Initial/Max: 120 mg tid	0.7–1.5 %	Hypoglycemia, headache, arthralgia, nausea, upper respiratory infections, constipation	Children, pregnancy, nursing, type 1 diabetes, ketoacidosis
Repaglinide (Prandin) 0.5, 1, 2 mg	Initial (depends on HbA1c): 0.5–1mg tid. Max: 16 mg/day			
Bromocriptine (Cycloset) 0.8 mg	Initial: 0.8 mg 2 h after waking in the morning. Max: 4.8 mg.	0.4–0.8 %	Nausea, fatigue, constipation, dizziness, rhinitis, headache.	Renal and hepatic failure, psychosis, type 1 diabetes, syncopal attacks, migraine headache.

of the mechanism of action of each drug, as well their advantages, contraindications, and side effects is essential to choosing the best drug or combination of drugs to achieve good glycemic control with minimal side effects, thus preventing acute and chronic complications of type 2 diabetes.

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# GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes

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## The Incretin Effect

The observation that the insulin secretion response was approximately two to three times greater with an oral glucose intake in comparison with the same amount administered intravenously gave rise to the term “incretin effect” [1].

Incretin hormones are “derived” from the intestine and belong to the glucagon superfamily. Two hormones are related to the incretinic effect: glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. The GIP is produced by K cells in the distal ileum and colon, while GLP-1 is secreted in L cells in the distal jejunum, ileum, and colon. Both are released in response to food intake and two to threefold increases in plasma levels, with peak values dependent on the amount

and type of food [2]. The GLP1 plasma levels increase a few minutes after the ingestion of food, suggesting that neural and endocrine mechanisms stimulate GLP-1 secretion even before L cell stimulation by nutrients [3]. The incretins are rapidly degraded by the DPP-IV enzyme found on the surface of epithelial and endothelial cells, as well as in plasma [4]. The half-life of GLP-1 is less than two minutes, while that of the GIP is around five to seven minutes [2]. The action of incretin occurs through its binding to specific receptors distributed systemically (pancreatic cells, gastrointestinal tract, central nervous system, heart, lungs, and kidneys) [2–5].

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## Biological Effects of GLP-1

### Pancreatic Effects

GLP1 binds to specific receptors on pancreatic beta ( $\beta$ ) cells and stimulates insulin-glucose production in a glucose-dependent manner [6]. It also regulates the production of other  $\beta$ -cell substances such as glucokinase and type 2 glucose transporter (GLUT-2) that enhance cell sensitivity to  $\beta$  glucose [7].

It has also been demonstrated that GLP-1 stimulates the differentiation of precursor cells into mature  $\beta$  cells, promotes their proliferation, and increases their resistance to apoptosis [8, 9]. However, it is important to remember that these effects were demonstrated by short-term studies. More data are needed to confirm whether chronic

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therapy with GLP-1 promotes sustained improvement in the quantity and function of the pancreatic  $\beta$ -cells [10].

GLP-1 acts on alpha ( $\alpha$ ) cells by inhibiting pancreatic glucagon secretion, also in a glucose-dependent manner [10]. More importantly, the counter-regulatory mechanisms are not affected, as a result of which glucagon release in the presence of hypoglycemia is preserved [11].

### Extra-Pancreatic Effects

Due to the broad distribution of GLP-1 receptors on various tissues, their activation is associated with a variety of extra-pancreatic effects, some of which are essential for glycemic control [10].

In animal models, GLP-1 inhibits hepatic glucose production and increases the production of glycogen [12]. There is an improvement in hepatic insulin sensitivity and reversal of hepatic steatosis. In humans there is an enhancement of the markers of hepatic damage [13, 14].

GLP-1 and GLP1 agonists exert their inhibitory actions on acid secretion and delay postprandial gastric emptying in a dose-dependent manner. The mechanisms involved in gastrointestinal effects are complex and have yet to be fully clarified. The decrease in the rate of gastric emptying is associated with lower levels of postprandial glucose and insulin, thus having an important impact on the normalization of glycemia [15].

The GLP-1 molecules are small, so they can cross the blood–brain barrier and activate specific brain receptors, particularly at the hypothalamic nucleus. Their actions in the central nervous system (CNS) include increased satiety and appetite suppression, resulting in weight loss [2]. Complementary mechanisms are suggested, such as vagal inhibition, induced gastric distension, and an increased feeling of fullness, contributing to the inhibition of hunger and weight loss [2, 5].

The cardiovascular effects of GLP-1 are probably cardio-protective, with actions such as a significant reduction of the cardiac infarct area, an improvement in glucose uptake by the myocardium and improved left ventricular function [16]. GLP-1 also results in an improvement in endothelial dysfunction and attenuation of atherosclerotic

plaque progression [17]. The effects on blood pressure are still uncertain, with some studies reporting small decreases in systolic and diastolic pressures, and others showing no benefits [10].

In relation to lipid metabolism, GLP-1 and GLP1 RA may have minor benefits, with a small reduction in LDL cholesterol and triglycerides and a moderate increase in HDL, probably related to weight loss [10].

### The Incretin Effect on Type 2 Diabetes

Unlike what was observed in healthy individuals, in diabetic patients there are no significant differences in C-peptide concentration (indirect measure of insulin production) between oral and intravenous glucose administrations [1]. This finding led to the conclusion that the incretin effect was absent or markedly reduced in type 2 diabetes and that this mechanism might be involved in the disease's pathophysiology and progression.

There have been many studies of GIP secretion in diabetic patients, and although no changes in its plasma concentration have been found, there is a clear reduction in the capacity to stimulate insulin secretion in DM2 [18]. There is a lot of controversy regarding changes to the GLP-1 in diabetic patients. Most studies indicate no reduction in the levels of GLP-1 in this population, but some subgroups, especially those with long-standing diabetes, may have changes in the postprandial secretion of this polipeptide [18].

### Exenatide

In the 1990s certain molecules that could cause hypoglycemia were described in the saliva of venomous lizards of the *helodermatideum* family. Those molecules were called “exendins.” Exendin-3 was present in the saliva of *Heloderma* *Horrindum* (lizard) and exandin-4 in that of *Heloderma* *Suspectum* (Gila monster). The molecules were nearly identical in their chemical structure, differing only in two amino acids. From the standpoint of biological activity, both acted on pancreatic acini, leading to cAMP production but,

unlike exendin-3, exendin-4 did not stimulate amylase or VIP release [19]. The therapeutic potential of these drugs has now begun to be considered. Exenatide is a synthetic version of exendin-4 [20, 21]. It is a peptide containing 39 amino acids and shares 53 % homology with native GLP1. It was the first drug of a new class of anti-hyperglycaemic drugs known as GLP1 RA which, together with the DPP-IV inhibitors, are known as “incretinomimetics” [22]. Exenatide has the same affinity for the GLP1 receptor as the native GLP1, but is much more resistant to degradation by the DPP-IV enzyme, and its presence can be detected in circulation 10 h after administration, while GLP1 is inactivated after 2 min [21–23]. This mechanism of exenatide allows it to be used twice daily.

It is marketed under the name *Byetta* [20], with 5- and 10-mcg doses. It was recently marketed as an extended-release preparation, under the brand name *Bydureon*, 2 mg with the same pharmacological properties. This is administered at weekly intervals [24].

The biological actions of exenatide are [21–23]:

1. Stimulating the production of insulin—Exenatide stimulates insulin secretion in a glucose-dependent manner recovering both first-phase (rapid initial 10–15 min) and second-phase insulin secretion. However, as previously mentioned, its insulinotropic effect is suppressed when blood glucose approaches 72 mg/dl, so the risk of hypoglycemia is very low, a property that clearly differentiates this class of drug from other hypoglycemic drugs
2. Suppression of glucagon secretion—Glucagon secretion is inappropriately elevated in type 2 diabetes and is deleted in a glucose-dependent manner by exenatide. In other words, when the patient has hyperglycemia, glucagon secretion is suppressed, while in the presence of hypoglycemia it is stimulated, enhancing the counter-regulatory response
3. Delayed gastric emptying
4. Reduction in food intake
5. Reduction in body weight
6. Beta cell proliferation—in animal models exenatide stimulated beta cell proliferation and neogenesis
7. Possible cardiovascular benefits (see extra-pancreatic effects of the GLP1 agonist)

Exenatide is administered subcutaneously 30–60 min before meals, with an interval of 6 h between doses. Following subcutaneous administration, the median concentration of exenatide was 211 pg/ml and the area under the curve was 1,036 pg.h/ml. Its half-life was 2.5 h, and the drug was detectable in the circulation 10 h after dosing. There was no difference in drug bioavailability whether injected in the arms, abdomen, or thighs. Likewise age, gender, weight, and ethnicity apparently did not significantly alter the kinetics of the drug. Elimination occurred predominantly by glomerular filtration followed by subsequent proteolytic degradation.

The slow-release exenatide (*Bydureon*) consists of microspheres of exenatide associated with a biodegradable polymer—“poly” (lactide-co-glycolide). The microspheres undergo a process of erosion, allowing a slow and continuous release of the drug. Its administration is weekly and the dose is 2 mg [23, 24].

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## Side Effects

Gastrointestinal effects—nausea, vomiting, and diarrhea—usually mild, were the most common side effects observed in clinical trials with exenatide, especially in the first month of treatment. Starting with low doses and gradually increasing the dose minimizes the frequency and intensity of symptoms [21, 23].

The risk of hypoglycemia was low when exenatide was used in isolation or associated with insulin sensitizers such as metformin or glitazones [25, 26]. Its use concomitantly with sulfonylureas increased the risk of hypoglycemia. When this association is the therapeutic option, the dose of sulfonylurea should always be decreased [27, 28].

An increase in reported cases of pancreatitis, in both its edematous and hemorrhagic forms, was associated with exenatide [29], but large recent databases did not confirm this association. It is well established that obesity and type 2 diabetes are risk factors for pancreatitis. Moreover, in this group of patients the presence of comorbidities such as hypertriglyceridemia and gallstones, other classic risk factors for pancreatitis,

is quite common. That is, this population is already at high risk for the condition. There is, however, a possible mechanism by which obesity and diabetes increase the risk of pancreatitis, namely the replication of pancreatic microduct stimulation, which triggers the formation of partially obstructed and distorted ducts, with flow obstruction, leading to inflammation and pancreatitis [30]. Since 2008 the FDA has been warning that patients on exenatide who experience abdominal pain, nausea, or vomiting should always be investigated for this condition [20, 22, 23].

In mice an increased incidence of medullary thyroid carcinoma, hitherto not understood in humans, was described. This finding could be explained by an increase in the GLP1 receptors of C cells in mice, which is about 10–12 times higher than that found in humans, which leads to the possibility of this effect being specific to mice [20, 21, 29].

Between 2005 and 2008, 78 cases of kidney failure associated with exenatide were reported, which generated an alert about the use of the drug in high-risk populations and pre-existing renal disease, especially for patients with CrCl between 30 and 60 ml/min/m<sup>2</sup>. The drug is contraindicated in patients with CrCl below 30 ml/min/m<sup>2</sup> [21, 23].

Approximately 45 % of patients who used exenatide developed antibodies against the molecule. The clinical significance of this finding is not yet fully understood. The occurrence of headache has also been more frequent with the use of exenatide [21, 23, 24].

To date, there is no evidence that exenatide increases cardiovascular risk [31]. In fact, it seems that the drug has cardio-protective effects: some animal studies have shown an improvement in cardiac output, an increase in left ventricle ejection fraction, decreased mean arterial pressure, increases in nitric oxide production with better myocardial perfusion and a diminished ischemic area. There are ongoing clinical studies designed to test this hypothesis. A meta-analysis published in the American Journal of Cardiology assessing the cardiovascular risk associated with the use of DPP-IV inhibitors, another class of drugs that also acts primarily in the “incretin system,” suggested cardiovascular protection [32].

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## Exenatide Twice Daily and Extended Release

In a head-to-head comparison between exenatide 10 mcg twice daily versus extended-release exenatide, 2 mg once a week, with 295 patients with type 2 diabetes, lasting 30 weeks, there were more patients with adequate control defined as HbA1c <7 % in the extended-release arm than in the conventional arm (2 daily applications), with no differences in relation to the risk of hypoglycemia or weight loss [33].

Exenatide caused greater reductions in HbA1c than glimepiride, sitagliptin, and glitazone when used in combination with metformin. Again, additional benefits were evidenced, such as weight loss and a low risk of hypoglycemia. Furthermore, side effects, especially gastrointestinal ones, were more frequent with exenatide and there were more dropouts in the group of patients who used the drug. Nevertheless, despite the greater number of dropouts, there were no observed differences regarding the occurrence of serious adverse effects [25–28, 34] (Tables 30.1 and 30.2).

Compared with insulin glargine and premixed insulin, exenatide was no less effective in achieving good glycemic control, with the best results in terms of hypoglycemia risk and weight loss. Once again, the patients using exenatide showed more side effects, especially nausea and vomiting [35–37].

A small trial evaluated the possibility of replacing glargin insulin with exenatide in type 2 diabetes patients. 61 % of patients who switched drugs were able to maintain good glycemic control. A shorter duration of type 2 diabetes and the use of low doses of insulin were significantly associated with a greater chance of success [38].

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## Liraglutide

Liraglutide was the second GLP-1 RA approved for use in type 2 diabetes. The native hormone has been modified to develop a compound with pharmacokinetic properties suitable for once daily administration.

**Table 30.1** Exenatide plus another T2DM drug: results of main trials

Drug	Rationale	Study design	Follow-up	Main Results	Side effects
Metformin [25]	Metformin plus placebo × metformin plus exenatide	Cohort. N = 150	82 weeks	Lower HbA1c and weight reduction with exenatide	More nausea and vomiting with exenatide
Sulfonylurea [27]	Sulfonylurea plus placebo × sulfonylurea plus exenatide	Randomized, double-blind. N = 337	30 weeks	Lower HbA1c and weight reduction with exenatide	More nausea, vomiting, diarrhea, and dose-dependent hypoglycemia with exenatide
Glitazones [34]	Exenatide plus glitazones × exenatide or glitazones plus metformin	Randomized, open. N = 137	20 weeks	Lower HbA1c and improved insulin sensitivity with exenatide plus glitazone	More nausea and vomiting with exenatide
Glargin insulin [36]	Exenatide × glargin insulin plus metformin or pioglitazone	Randomized, double-blind. N = 262	24 weeks	Weight loss and no hypoglycemia with exenatide: no HbA1c differences	More nausea, vomiting, diarrhea with exenatide

**Table 30.2** Head-to-head trials: exenatide × other drugs for T2DM

Drug	Rationale	Study design	Follow-up	Main results	Side effects
Sulfonylurea [28]	Exenatide × sulfonylurea plus metformin	Randomized, single-blind. N = 1,029	236 weeks	Lower HbA1c, weight loss, and less hypoglycemia with exenatide	More nausea, vomiting, diarrhea, and dropouts with exenatide.
Pioglitazone [26]	Exenatide plus metformin × pioglitazone plus metformin	Randomized, double-blind. N = 491	26 weeks	Lower HbA1c and weight loss with exenatide	More nausea and diarrhea with exenatide.
Sitagliptin [26]	Exenatide plus metformin × sitagliptin plus metformin	Randomized, double-blind. N = 491	26 weeks	Lower HbA1c and weight loss with exenatide	More nausea and diarrhea with exenatide
Insulin, glargin [35]	Exenatide plus metformin × glargin insulin plus metformin	Randomized, single-blind. N = 69	52 weeks	No differences in HbA1c between drugs. Weight loss and improved insulin secretion with exenatide	More nausea, vomiting, diarrhea with exenatide
Insulin, glargin [38]	Switching glargin insulin plus metformin for exenatide plus metformin	Randomized, open. N = 49	16 weeks	61 % patients could maintain a good glycemic control after switching from glargin insulin to exenatide	More nausea and vomiting with exenatide
Premixed insulin [37]	Exenatide plus metformin × premixed insulin plus metformin	Randomized, open. N = 501	52 weeks	No differences in HbA1c between drugs. Weight loss and less hypoglycemia with exenatide	More nausea, vomiting, diarrhea, and dropouts with exenatide

It is available for subcutaneous use in a single daily dose. It exhibits a 97 % structural similarity to endogenous GLP-1, and has a half-life of approximately 13 h. This pharmacokinetic pro-

file is due to the combination of prolonged absorption at the site of injection, a rate of albumin binding greater than 98 % and a high resistance to degradation by DPP-IV [39].

**Table 30.3** Summary of LEAD trials

Trial	Liraglutide-associated drug	Comparison	Study design	Main end point/follow-up	Summary
LEAD 1 [42]	Glimepiride	Liraglutide versus rosiglitazone or placebo plus glimepiride	Double-blind, randomized. N=1,041	HbA1c—26 weeks	Lower HbA1c with liraglutide (1.2 or 1.8 mg) than placebo or rosiglitazone when added to glimepiride
LEAD 2 [40]	Metformin	Liraglutide plus metformin versus metformin plus glimepiride	Randomized, controlled, open. N=1,091	HbA1c—26 weeks	Lower HbA1c with liraglutide than glimepiride when added to metformin
LEAD 3 [43]	Placebo	Glimepiride 8 mg versus liraglutide 1.2 or 1.8 mg plus placebo	Double-blind, randomized. N=746	HbA1c—52 weeks	Lower HbA1c and with liraglutide than glimepiride. More side effects with liraglutide
LEAD 4 [45]	Metformin plus rosiglitazone	Liraglutide 1.2/1.8 mg versus placebo metformin, plus rosiglitazone and metformin	Double-blind, randomized. N=533	HbA1c—26 weeks	Lower HbA1c, increase in C peptide and dose-dependent weight loss with liraglutide than placebo
LEAD 5 [44]	Metformin plus glimepiride	Liraglutide versus placebo versus glargin insulin plus metformin and glimepiride	Randomized, open, multicenter. N=581	HbA1c—26 weeks	Lower HbA1c, more weight loss, and less hypoglycemia with liraglutide. More side effects with liraglutide
LEAD 6 [41]	Metformin, glimepiride, or both drugs	Liraglutide versus exenatide plus metformin, glimepiride or both drugs	Randomized, open, multicenter. N=464	HbA1c—26 weeks	Liraglutide reduced mean HbA1c significantly more than exenatide

The trials for the approval of liraglutide comprised the LEAD program (Liraglutide Effect and Action on Diabetes), which included six large randomized controlled trials, with a total of over 4,000 patients, conducted in over 600 centers in 40 countries [40–45]. The objectives of the LEAD studies were to evaluate the efficacy and safety of liraglutide and compare it with other treatments available for type 2 diabetes. The summary of the studies is found in Table 30.3.

In relation to glycemic control, a significant and sustained HbA1c reduction of around 1.1–1.5 % was obtained in all studies. Liraglutide also showed a lower risk of hypoglycemia. All the LEAD studies showed a significant reduction in body weight of approximately 1.0–3.2 kg. A reduction in systolic blood pressure of about 2.1–6.7 mmHg was also observed. The possibility of an improvement in metabolic control associated with decreased body weight is of paramount

importance in the current scenario of a growing global prevalence of obesity and the forecast significant increase in the number of diabetics.

Liraglutide is, in general, well tolerated. The most common adverse events were related to the gastrointestinal tract, including nausea, vomiting, and diarrhea, occurring in 10–40 % of patients participating in the studies cited above. Most cases were mild and transient, occurring early in treatment and rarely resulting in discontinuation of the medication.

The effect on thyroid C cell in humans is unclear, since there are fewer C thyroid cells than in mice and the expression of GLP-1 receptors on those cells is very low [46]. A study was carried out to compare the levels of plasma calcitonin in humans using liraglutide versus a control group, and after two years of follow-up there were no consistent differences between the two groups, supporting the hypothesis that this drug does not

increase the risk of follicular thyroid carcinoma in humans [47]. Until more definite data become available, the U.S. Food and Drug Administration (FDA) does not recommend its use in patients with a past or family history of medullary carcinoma of the thyroid or multiple endocrine neoplasia (MEN) type 2A or 2B.

Among the LEAD studies, there were seven cases of pancreatitis reported in 4,257 patients using liraglutide, while in the comparator group there were 2 cases. The small number of events hinders a proper conclusion involving causality. As previously mentioned, it is well established that diabetic patients show an increased risk of pancreatitis, a risk that can be three times higher than in the nondiabetic population, complicating data interpretation. The current recommendation of the FDA is to monitor the occurrence of abdominal pain and to immediately suspend the use of liraglutide use if pancreatitis is suspected.

In the LEAD studies, liraglutide was associated with a lower rate of major cardiovascular events compared with other therapies which served as comparators. It is possible that the beneficial effects of liraglutide on glycemic control, weight loss, and reduction in systolic blood pressure contributed to this result, but long-term studies are still being conducted to establish whether there are any real cardiovascular benefits.

Liraglutide is used initially at a dose of 0.6 mg, with progression to 1.2 mg. This gradual progression helps to minimize the side effects. To achieve a better glycemic control, it can be used at a dose of 1.8 mg. There is no need for dose adjustment according to age, gender, or ethnicity. It should be used with caution in patients with liver and kidney failure, although its pharmacokinetics do not change significantly in the presence of advanced renal failure.

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### **The Role of GLP1 RA in the Modern Treatment of T2DM**

At the 2012 ADA/EASD position statement the indications for incretin-based therapies were greatly expanded in comparison with the previous document. In patients poorly controlled

despite a proper diet, physical activity, and monotherapy with metformin, if the main objectives are to achieve good glycemic control with a low risk of hypoglycemia and leading to weight loss, GLP1 RA should be the first choice, although the costs and potential side effects should always be taken into consideration [48].

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### **GLP-1 RA in the Treatment of Obesity**

The World Health Organization estimates that the worldwide prevalence of overweight is 1.5 million adults, while 500 million are believed to be obese. It is known that the risk of developing T2DM is directly proportional to excessive body weight, increasing approximately threefold in overweight patients and 20-fold in obese ones when compared to individuals with a normal body mass index (BMI) [49]. Obesity, particularly when associated with increased visceral adipose tissue, is an independent risk factor for coronary heart disease, contributing to a substantial increase in cardiovascular morbidity and mortality. Considering that there is a global trend towards an increased prevalence of obesity and T2DM and that the therapies most widely available for T2DM induce weight gain (insulins, thiazolidinediones, sulfonylureas), the prospect of drugs that act in glycemic control, leading to a better metabolic profile, is quite encouraging.

Studies with GLP-1 in diabetic patients showed metabolic benefits, including weight loss, with a negligible risk of hypoglycemia when used as monotherapy, due to glucose-dependent insulin release. The proposed mechanisms to induce weight loss involve delayed emptying gastric, leading to early satiety and appetite suppression at the level of the CNS. Such features have raised the possibility of using these agents for treating obesity in nondiabetic patients, driven by the limited therapeutic arsenal currently used for this purpose.

A meta-analysis of 21 studies involving GLP-1 analogues in obese or overweight diabetic and nondiabetics was performed and it was found that there was a weight loss in all studies [50].

The mean weight reduction obtained with the highest dose of GLP-1 RA ranged from  $-0.2$  to  $-7.2$  kg. Patients without diabetes had a greater weight loss than diabetics (mean,  $-3.2$  kg versus  $2.8$  kg). There were no differences in change in body weight between exenatide and liraglutide or between short-acting exenatide and slow-release exenatide. The results suggest that treatments with GLP-1 agonists are an effective intervention for overweight or obese patients, irrespective of the presence of T2DM.

The study on long-term safety, tolerability, and sustained weight loss with liraglutide in nondiabetics was reported after two years of follow-up [51]. The patients studied were obese (BMI 30–40), nondiabetic, aged 18–65, enrolled in a program of diet and exercise associated with liraglutide (2.4/3.0 mg), placebo, or orlistat. Weight loss with liraglutide was 7.8 kg, which is better than placebo and orlistat, and sustained over two years. Over 70 % of patients taking liraglutide maintained a weight loss greater than 5 % relative to baseline, which was associated with an improvement in cardiovascular risk factors and metabolic changes. There was an improvement in systolic blood pressure, a decreased prevalence of diabetes (over 50 %) and an improvement in body composition, with loss of adipose tissue and decreased waist circumference. Tolerability was good and adverse events were mostly mild or moderate, in particular nausea and vomiting, which were much more common than with placebo, as described in other studies. There was no decrease in adherence due to the fact that it is an injectable medication. The results of this study are very important in corroborating the safety and efficacy of liraglutide.

## Lixisenatide

Lixisenatide is a GLP-1 receptor agonist derived from exenatide which is available in Europe for clinical use [52]. It has a more pronounced effect on PPG, mainly after the first meal of the day, and is labeling for once daily 20 micrograms subcutaneous injections. The effects on decreasing HbA1c and body weight however are less than with liraglutide administration. Lixisenatide is

undergoing clinical development as a combination product with insulin glargine. This treatment combination has been shown to substantially improve HbA1c, without significant weight gain, in the GetGoal-L, GetGoal-L-Asia, and the GetGoal- Duo 1 studies. At present, unless lixisenatide is priced lower than the already available GLP-1RA alternatives, it appears that the main place in therapy for lixisenatide is in the combination with insulin glargine. There is also an ongoing multicenter study for the evaluation of cardiovascular outcomes in patients with Type 2 diabetes after acute coronary syndrome during treatment with lixisenatide.

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### Therapy with Insulin in Type 1 Diabetes and Type 2 Diabetes Inpatient

The benefits achieved in the long term, with a more rigorous metabolic control in preventing and reducing chronic complications of diabetes mellitus (DM) were strongly established in both type 1 diabetes (T1D) and type 2 (T2D). Large prospective studies, such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Survey Study (UKPDS), about the influence of metabolic control on the incidence of microvascular and macrovascular chronic complications of diabetes published in the nineties, established that a reduction of 1 % of the glycated hemoglobin (A1c) levels influences significantly the protection of microangiopathy and neuropathy [1, 2].

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### Insulin Therapy in Type 1 Diabetes

The aim of the treatment of Type 1 diabetes (T1D), both at onset and years after the diagnosis, is the maintenance of near-normoglycemia to prevent the onset or delay progression or both of long-term complications [1, 3, 4]. The data from the Diabetes Control and Complications Trial (DCCT) suggest that residual b-cell function is associated with improved outcomes, with better glycemic control and lower risk for hypoglycemia and long-term chronic complications [5].

The beneficial and protective effects achieved with intensified insulin control in the prospective DCCT study were clear and remained in the Epidemiology of Diabetes Intervention and Complications (EDIC) study, despite the augment of A1c levels, over the follow-up period. However, there is still a gap between evidence and clinical medical practice, since the majority of diabetes patients do not achieve the optimal goal. In 2009, DCCT/EDIC study demonstrated that 81–87 % of patients with diabetes had glycated hemoglobin A1c levels >7.0 % [6] and these results were also showed in UK study where 74 % of patients have A1c >7.5 % [7]. This fact emphasizes that glycemic control is still not satisfactory, in part due to less than optimal insulin therapy.

The recommended therapy for T1D consists of intensive insulin treatment, using multiple daily insulin injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII) therapy; matching of prandial insulin to carbohydrate

intake, blood glucose tests, and physical activity. The goal of the T1D treatment is to keep blood glucose levels throughout the day near normal limits, avoiding hypoglycemia and glucose variability [8, 9]. The American Diabetes Association (ADA) recommends glycemic targets of fasting and preprandial blood glucose between 90 and 130 mg/dL and 2-h postprandial <180 mg/dL and A1c <7.0 % [10]. In children under 13 years of age, elderly patients (>65 years), a history of unawareness hypoglycemia, comorbidities or severe macrovascular disease, the glycemic targets can be more flexible, and it is acceptable to maintain blood glucose fasting and preprandial between 80 and 160 mg/dL and postprandial >200 mg/dL and, A1c levels by up to two percentage points above method [10]. Pregnant women should maintain lower blood glucose levels, between 60 and 90 mg/dL if fasting and preprandial, <120 mg/dL postprandial and normal A1c. The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends maintaining for children and adolescents fasting or preprandial blood glucose levels between 90 and 145 mg/dL, postprandial between 90 and 180 mg/dL, at bedtime between 120 and 180 mg/dL and nocturnal between 80 and 162 mg/dL [11, 12], although the treatment goals should be individualized, taking into account the patient's age and the risk of hypoglycemia, especially nocturnal and unawareness.

Different therapeutic schedules have been used over the years in the management of patients with T1D [13–15]. Due to the pharmacokinetic profile of the intermediate-acting neutral protamine Hagedorn (isophane insulin; NPH), the conventional treatment with NPH once or twice a day does not mimic the pattern of endogenous basal insulin secretion and may cause hypoglycemia during its peak of action and hyperglycemia 10–14 h after its administration.

The physiologic insulin replacement attempts to mimic normal insulin secretion. Generally, physiologic regimens replace basal and prandial insulin (often referred to as “bolus”) separately. The basal insulin is responsible for avoiding lipolysis and hepatic glucose release in the interdigestive period; a prandial insulin and additional

**Table 31.1** Insulin doses at different ages and periods

	Dose (U/kg/day)
Honey-moon period	<0.5
At diagnosis or after Ketoacidosis	0.5–1.0
Prepubertal	0.7–1.0
Pubertal	1.0–2.0
Sick days	1.2–1.5
Basal insulin	40–60 %

doses of insulin to correct the preprandial hyperglycemia or those that occur during the inter-food period. The prandial insulin mimics the response of endogenous insulin secretion to food intake. This physiological response induces a rapid and intense insulin secretion (first phase) followed by a more prolonged secretion into the portal circulation (second stage).

The total daily insulin dose for patients with newly diagnosed of T1D or recent diagnosis of ketoacidosis recommended varies from 0.5 to 1.0 U/kg/day. However, sometimes higher doses of insulin are required to recover metabolic balance [16–20]. The daily insulin dose depends on age, body weight, pubertal stage, duration and stage of diabetes, local insulin administration, carbohydrate intake, self-monitoring and A1c levels, daily routine and presence of acute complications, as infections or sick days [21]. At the partial remission phase, the daily total insulin dose is generally <0.5 U/kg/day and subsequently, after this phase, the daily requirement of insulin increases from 0.7 to 1.0 U/kg/day in prepubertal children and can reach 1.0–2.0 U/kg/day during puberty [21] or at stress situation (physical or emotional) from 1.2 to 1.5 U/kg/day. These data are summarized in Table 31.1.

Usually, in the first 6 months of the T1D diagnosis, there is a period denominated “honeymoon period,” characterized by the normalization of blood glucose levels, being recommended to maintain small amounts of insulin during this period, since it lasts from several weeks to months [16–20]. There is evidence that in young T1D adults, the initial phase of the disease is progressive and characterized by a slow decline of beta-cell function compared to children and adolescents [22]. Interesting data were also obtained

from the DCCT study, suggesting that the persistence of residual beta cells function is associated to better outcomes, such as improved glycemic control, lower risk of hypoglycemia, and less long-term chronic complications [1, 5, 23, 24], indicating intensive treatment (basal-bolus) since the beginning of the diagnosis.

The intensive insulin treatment is achieved by using multiple daily insulin injections (MDI): three to four injections per day of basal and prandial insulin or continuous subcutaneous insulin infusion (CSII) therapy (insulin pump) [16–20]. The metabolic control (A1c) obtained with CSII is slightly better than multiple daily injections, however, both are appropriate and effective [25]. This treatment (MDI) can be obtained using NPH insulin (two to four times a day: before breakfast and bedtime, or before breakfast, lunch, and bedtime, or before breakfast, lunch, dinner, and bedtime) or insulin glargine (once daily: before breakfast or lunch or dinner or bedtime) or insulin detemir (once or twice a day: before breakfast and/or dinner and/or bedtime) associated with fast-acting insulin (regular) administered half an hour before meals or fast-acting insulin analogues (lispro, aspart, and glulisine) administered before meals or even after meals [16–20, 26, 27]. The effectiveness of these analogues after meals is at least comparable with the administration of regular insulin before meal [28–30], making it possible to administer in young children just after the carbohydrate ingestion. When regular insulin is administered 5 min before meals, it is less effective than 10–40 min before because of its profile action.

Long-acting insulin analogues (glargine and detemir) are approved for use in children with at least 6 years of age [31–33], although there are several reports demonstrating the security and efficacy in younger children, even below six years of age [31–33]. The comparison of multiple daily NPH insulin with glargine in patients 5–16 years showed that patients treated with insulin glargine had a lower fasting glucose, with similar A1c levels.

Perhaps, the most important benefit of using long-acting insulin analogues is the reduction of the hypoglycemic events, mainly nocturnal hypoglycemia. Moreover, it has been reported that the

use of these analogues reduces the occurrence of severe hypoglycemia (seizures, loss of consciousness, or need of assistance of another person to give carbohydrate). The use of long-acting analogues is associated with lower frequency of hypoglycemia, so they are recommended in younger children, who are under neurodevelopment growth, and the harmful effects of the recurrence of severe hypoglycemia may cause permanent damages to the central nervous system [34–36].

Classically, the intensive treatment is obtained by the administration of NPH insulin twice a day, using around 70 % in the morning and 30 % at bedtime, associated with three daily applications of fast-acting human insulin or fast-acting analogues. Other form, is to administer NPH insulin three times per day, about 50 % by morning (70 % NPH and 30 % fast-acting), approximately 25 % at lunch (60 % NPH and 40 % fast-acting), the remaining 25 % at bedtime [37–40]. It is also possible to administrate NPH insulin four times per day, about 30 % of the dose by morning (70 % NPH and 30 % fast-acting), approximately 30 % at lunch (60 % NPH and 40 % fast-acting), 20 % at dinner (90 % NPH and 10 % fast-acting), and the remaining 20 % at bedtime (NPH at bedtime only) or approximately 0.2 U/kg. Nevertheless it is important to remember that insulin pump treatment has contributed to understanding basal-bolus regimen, and today it is recommended that the percentage of basal and bolus insulin should be similar, being recommended that the basal insulin dose should be 40–60 % of the total dose prescribed.

Intensive treatment can also be achieved by replacing the NPH insulin to glargine (once daily) or detemir (once or twice daily) insulin. The replacement of NPH insulin to glargine is performed by reducing the basal dose of insulin by 20 % and was subsequently adjusted as the results of fasting blood glucose. The replacement of NPH to insulin detemir requires no decrease in insulin dose previously used, but may require two applications per day [33]. The administration of glargine insulin before breakfast, dinner or bedtime had been compared and data showed lower episodes of nocturnal hypoglycemia when the

administration was before breakfast, despite the association to a slight increase of fasting glucose.

Hypoglycemia is the most common adverse effect of intensive insulin therapy and is defined by a glucose value  $<70$  mg/dL. In the Diabetes Control and Complications Trial, intensive therapy increased the risk of severe hypoglycemia. The events were reported by 26 % of patients with a mean of 1.9 episodes per patient per year, and 43 % of episodes occurred nocturnally.

The insulin adjustment is held from fasting plasma glucose and self-monitoring blood glucose, preprandial and postprandial [16–19]. All patients with T1D should perform the self-monitoring of blood glucose tests, and the American Diabetes Association suggests three or more tests per day [41]. The dose of NPH insulin at bedtime is adjusted according to the blood glucose tests at fasting and the other doses by the preprandial results, adjusted every 3 or 4 days. The adjustments of insulin long-acting analogues are done by the fasting blood glucose levels and at least every 5–7 days. The fast-acting human insulin and analogues doses are adjusted by the results of the blood glucose tests 2 h post-meals, considering the sensibility factor and the carbohydrate intake.

Intensive treatment can also be obtained with biphasic insulin, but its use in T1D presents some drawbacks due to lack of flexibility of better adjustments, leading to greater risk of hypoglycemia. However, the use of biphasic insulin may be useful in patients with visual or motor restrictions or those denying multiple daily injections [42].

There are different strategies for the management of insulin and blood glucose control during physical activity [43]. The reduction of the basal insulin or the fast-acting insulin pre-exercise, extra carbohydrate ingestion, or the reduction of basal insulin after exercise are strategies that can be implemented and have advantages and disadvantages. Reducing the NPH or long-acting analogues doses in 20–60 % and reducing fast-acting insulin by 30–50 % pre-exercise may be necessary, depending on the intensity of the exercise and this reduction can reach even up to 90 % [43].

There are many barriers in order to achieve adequate glycemic control in type 1 diabetes,

including the occurrence and fear of hypoglycemic events, complexity of the day-to-day management and, particularly, the need for self-monitoring and frequent insulin adjustments. These challenges cause a large impact on quality of life of patients and considerable costs to health [44]. It is expected that in some years, we will be able to prevent these conditions with advances in new techniques and therapeutic agents. However, at the present the most important issue is to help patients with T1D deal with their disease properly, reducing the occurrence of acute and chronic complications and improving their quality of life.

## Insulin Therapy in Type 2 Diabetes

Randomized controlled clinical trials that compared intensive to conventional treatment in T2D, such as the United Kingdom Prospective Diabetes Survey (UKPDS) and the Kumamoto Study, established glycemic targets of diabetes treatment associated to better long-term outcomes. Although these studies present different epidemiological data, clinical interventions and outcomes, all agree with the fact that the reduction of blood glucose is effective in decreasing microvascular and neuropathic chronic complications.

The UKPDS study, that evaluated 5.112 T2D patients during 20 years, demonstrated a decrease in chronic complications with intensive treatment, with a reduction of approximately 1 % in A1c levels (7.9–7.0 %), resulting in a 25 % reduction in the risk of microvascular complications and 16 % of acute myocardial infarction in 10 years [2], and also demonstrated benefits of the intensive blood pressure control [45].

Another study (STENO-2), with T2D in intensive care, with A1c goals of  $<6.5$  %, blood pressure  $<130/80$  mmHg, statin use (total cholesterol  $<180$  mg/dL and LDL  $<100$  mg/dL) and inhibitors of angiotensin-converting enzyme (in cases of persistent microalbuminuria), showed a 53 % reduction in the risk of cardiovascular events [46].

The DECODE study showed that postprandial hyperglycemia is an independent risk factor for mortality [47]. Mainly, the prevention of microvascular and macrovascular complications in

T2D patients requires tight control of fasting, preprandial and postprandial blood glucose, A1c, lipids, and blood pressure. However, in older patients with previous cardiovascular disease and longstanding diabetes, the glycemic control may not be so strict, as demonstrated by the ACCORD study, which showed an increase in cardiovascular mortality and other causes in T2D patients in intensive care [48].

The ADA recommends the targets for T2D treatment, preprandial glucose between 90 and 130 mg/dL and A1c levels <7.0 % [49, 50]. However, the American Association of Clinical Endocrinologists (AACE) [51] and the International Diabetes Federation (IDF) [52] suggest A1c levels <6.5 %. To achieve these goals, the proper maintenance of fasting glucose, in addition to postprandial glucose through basal-bolus insulin, is an important factor in the treatment of subjects with T2D [53].

The pathophysiology of pharmacological treatment of subjects with T2D depends on various aspects contributing to hyperglycemia. The peripheral insulin resistance (adipocytes and skeletal muscle), presented in 85–90 % of the cases [53], the deficiency of the insulin production by the beta cell and the excessive hepatic glucose production caused by the insulin resistance, are all contributor factors to the onset of hyperglycemia. As shown in UKPDS, the persistence of elevated levels of A1c leads to progressive loss of beta cell function in secreting insulin [2].

The T2D treatment begins with monotherapy and subsequently a second drug is added and, if necessary, a third oral drug or insulin is implemented. However, the new consensus algorithm, proposed by both societies (ADA and EASD) recommend that insulin might be implemented earlier, shortly after oral monotherapy. This treatment initially begins by changes in lifestyle (diet, cholesterol control, weight reduction, pressure control, physical activity and tobacco control) associated to metformin [54]. If these interventions are not effective in reducing A1c levels <7.0 %, another approach must be implemented 3 months after the initiation of metformin. However, there is no consensus on the second drug used, being insulin, sulfonylurea, thiazoli-

dinedione (pioglitazone), or DPP-4 inhibitors, some of the treatment options available.

Insulin could be indicated as a second drug added after metformin, when the patient presents intense clinical evidence (polyuria, polydipsia, polyphagia, weight loss) of decompensation and/or A1c  $\geq 8.5$  %. However, if the clinical evidence is less intense, and/or A1c levels <8.5 %, another oral drug can be added before using insulin.

To start insulin therapy in T2D patients, it is recommended to start with 10 U (or 0.2 U/kg of body weight) of a basal insulin (NPH, glargine or detemir) at bedtime, maintaining the oral antidiabetic agents already being used [55]. In a study comparing the use of glimepiride associated with insulin glargine in the morning or at bedtime or bedtime NPH insulin in 695 patients with T2D, A1c levels decreased 1.24 % with glargine in the morning, 0.96 % using glargine at bedtime and 0.84 % using NPH insulin at bedtime [56]. The improvement in A1c was more evident with glargine in the morning than at bedtime ( $p=0.008$ ) and than NPH at bedtime ( $p=0.001$ ).

The randomized Treat-to-Target study, which compared insulin glargine or human NPH insulin to oral therapy in subjects with T2D, showed similar results of A1c levels (6.96 % vs. 6.97 %) and fasting glucose (117 mg/dL vs. 120 mg/dL) [57]. The insulin adjustment was performed every 3 days, according to the blood glucose tests. In the LANMET study, with T2D patients with inadequate glycemic control, on use of oral antidiabetics (90 % with sulfonylureas associated to metformin) and without previous treatment with insulin, 110 subjects were randomized to receive insulin glargine at bedtime plus metformin or NPH insulin plus metformin for 36 weeks [58]. The initial dose of insulin was 10 U for those using previously only metformin and 20 U for those using metformin associated with sulfonylurea. The individuals randomized to receive insulin glargine showed lower fasting plasma glucose than NPH group (103.5 mg/dL vs. 107.3 mg/dL,  $p<0.001$ ) [58]. In this study, the insulin dose was increased by 2 U every 3 days if the fasting plasma glucose (FPG)  $\geq 100$  mg/dL within 3 days and 4 U if FPG  $\geq 180$  mg/dL in the same period, and successively. The patient was

responsible for his insulin adjustment or self-titration, maintaining their optimal dose without endocrinologist visits and telephone calls.

In the UKPDS, patients with T2D receiving insulin therapy had lower A1c levels, but 1.0–2.0 % more patients receiving insulin reported at least one episode of severe hypoglycemia per year than those patients receiving other therapies. Intensive therapy, with oral medications or insulin, has been shown to increase the risk of episodes of hypoglycemia.

The GOAL study, involving 7,893 patients with T2D, uncontrolled on oral antidiabetic randomized to four treatment groups with long-acting insulin analog glargine, involving different forms of titration and different ways of measuring A1c, found significant reductions in A1c and blood glucose in all groups ( $p < 0.0001$ ) [59]. However, the group with active titration showed a greater reduction in A1c than those with usual titration (1.5 % vs 1.3 %,  $p < 0.0001$ ) and a greater proportion of patients achieved an A1c  $< 7.0$  % (38 % vs. 30 %,  $p < 0.0001$ ) [59].

In patients with T2D using only one dose of NPH at bedtime, it is possible to use twice a day (morning and bedtime) when goals are not being achieved, before starting to use fast-acting insulin. When the basal insulin at bedtime or twice a day associated to oral antidiabetics is no longer sufficient to maintain A1c levels  $< 7.0$  %, it is necessary to intensify insulinization. This means starting with fast-acting insulin (human or analogues), maintaining the basal or biphasic insulin. When insulinization is intensified, oral insulin secretagogues (sulfonylurea, glinides) must be suspended, but metformin is maintained.

In T2D, a study using insulin glargine as basal insulin demonstrated that a fast-acting insulin could be started initially at the main meal, as it causes the greatest increase in postprandial glycemia, or results in the highest elevation of pre-meal glucose, then extending this insulin to the other meals, if necessary, to achieve A1c goal [60].

In a study with T2D uncontrolled patients at diagnosis, which compared the use of NPH insulin at bedtime plus regular insulin before meals and NPH plus lispro, the use of the insulin analog

showed to be superior in achieving metabolic control, with suppression of glucagon secretion and reduction of the glucotoxicity [61]. Another study also observed that use of insulin lispro in patients with T2D, administered before meals, was more effective in reducing A1c than the use of metformin or NPH insulin at bedtime. In a study comparing the insulin analogues lispro and aspart, the results evidenced that both have the same effectiveness in controlling postprandial glucose excursions [62]. The administration of insulin aspart 15 min after the meal is as or more effective in controlling postprandial hyperglycemia than implementing the regular insulin before meals [28]. Greater predictability of action and lower glycemic variation with the use of these analogues have also been described in individuals with T2D [63]. Individuals with T2D treated for 26 weeks with the long-acting analog insulin detemir associated to aspart insulin before meals, showed glycemic control comparable to those treated with NPH and aspart. However, as demonstrated in other studies, there was less variability between individuals, and less weight gain with insulin detemir [64, 65].

Regarding the use of biphasic insulin in subjects with T2D, studies demonstrated that the biphasic analogues are more effective in reducing the postprandial hyperglycemia than those containing NPH and regular, without significant reduction of A1c [66, 67]. However, the improvement of postprandial hyperglycemia and glycemic variability reduction, despite A1c levels, may be important factors in reducing the risk of onset and progression of microvascular and macrovascular chronic complications. The use of biphasic insulins (premix) may be recommended for those patients with the greatest difficulty in assimilating the basal–bolus regimen, considered apparently to be more convenient because the doses are already previously divided on a fixed percentage of basal and fast-acting insulin analogues 70/30, 75/25, or 50/50.

When patients with T2D need to use basal–bolus regimen, as in T1D, meaning that these patients have severe insulinopenia, and glucose variability occurs frequently, continuous subcutaneous insulin infusion could be indicated.

## Inpatient Insulin Therapy

Hyperglycemia is a common acute complication of critically ill patients, during hospitalization at intensive care units (ICUs). Some studies demonstrated that the presence of hyperglycemia, in particular severe hyperglycemia, is associated with increased morbidity and mortality in some patients, but some clinical and randomized trials evaluating the effects of tighter glucose on the mortality of critically ill patients showed conflicting data.

Despite these conflicting evidences, the American Diabetes Association, the American Association of Clinical Endocrinologists, Brazilian Diabetes Society, and other professional organizations recommend intensive insulin therapy as the standard of care for critically ill patients [68–70].

The main barrier to implement a tight glucose control in patients during hospitalization and critically ill, is the increased risk of severe hypoglycemia that has been described to be associated to increase mortality. Because of these aspects and risks or benefits, the tight glucose control is used infrequently by some clinicians. The Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, an international multicentre trial involving 6,104 patients, largest randomized clinical trial of intensive insulin therapy, evidenced that blood glucose target  $\leq 180$  mg/dL is associated to lower mortality than did a target of 81–108 mg/dL [71].

It is recommended that all clinicians assess all patients admitted to the hospital for a history of diabetes. When present, this diagnosis should be clearly identified in the medical record. All patients, independent of a prior diagnosis of diabetes, have laboratory blood glucose (BG) testing on hospital admission. The patients without a history of diabetes with BG greater than 7.8 mmol/L (140 mg/dL) should be monitored with bedside capillary BG testing for at least 24–48 h. Those with BG greater than 7.8 mmol/L require appropriate therapeutic intervention [68].

The inpatient care of individuals with diabetes and hyperglycemia is complex, involving multi-

ple providers with varying degrees of expertise who are dispersed across many different areas of the hospital. Multidisciplinary local protocols should guide safe glycemetic control, hypoglycemia prevention, and patient preparation for care transitions. Poor coordination of glucose monitoring, meal delivery, and insulin administration is a common barrier to optimal care of the patients during the hospitalization period.

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## Protocol for Insulin therapy in Critical Ill Patients

The most efficient and safe therapeutic option to treat critically ill patients is by continuous intravenous insulin pump infusion [72]. It is recommended preferably to use regular human insulin than fast-acting analogues, in solutions containing 100 U diluted in 100 mL of 0.9 % saline solution (1 U/mL).

Some authors recommend an initial intravenous bolus of insulin before starting the infusion, to reduce the glucotoxicity if glycemia is greater than 300 mg/dL, using a standard formula to correct the hyperglycemia (glycemia  $300 \div 100 =$  insulin dose). The initial infusion rate can be calculated by Rate infusion (mL/h) = Current Glycemia – Minimal Glycemia  $\times$  Correction Factor (CF). The minimal of blood glucose depends on each case and may be established at 100 mg/dL. The CF depends on the patient's estimated insulin resistance; is common to start with a factor of 0.02, rising 0.03–0.05 in those with more insulin resistance or reducing to 0.01 in patients more sensitive to insulin.

The infusion rate should be adjusted to maintain blood glucose at target, noting that the prompt glucose decline should be avoided, reducing the rate of insulin infusion and, in the presence of hyperglycemia, the rate must be accelerated. Thus, the dynamic behavior of glycemia, analyzed the last three measures, it is important to adjusting the rate of insulin infusion. Glucose measurements during insulin infusion should be performed initially every hour, and in those with glycemetic control at target, every 2 or 3 h.



It is important to avoid glycemc variability in these patients critically ill, because there is an increase of the mortality, independent of the glucose variation, induced by the cellular oxidative stress.

### Protocol for Insulin therapy in Non-critical Ill Patients

Some studies demonstrated that the presence of hyperglycemia in non-critical ill patients also increases morbidity and mortality [68–70].

It is recommended that only patients with T2D well controlled maintain oral antidiabetic agents, and the others should discontinue oral diabetes drugs and non-insulin injectable diabetes medications upon hospital admission.

To start insulinization in these patients, the dose could be calculated at a total daily dose of 0.2–0.3 U/kg of body weight in patients with aged  $\geq 70$  years and/or glomerular filtration rate less than 60 mL/min or 0.4 U/kg of body weight per day for patients not meeting the criteria above who have BG concentrations of 7.8–11.1 mmol/L (140–200 mg/dL) or 0.5 U/kg of body weight per day for patients not meeting the criteria above when BG concentration is 11.2–22.2 mmol/L (201–400 mg/dL).

The total calculated dose is distributed approximately as 50 % basal insulin and 50 % prandial insulin. If the basal insulin is glargine or detemir give it once a day or twice if detemir or NPH is given, at the same time each day and the fast-acting (prandial) insulin should be given in three equally divided doses before each meal. If the patient is not able to eat, it is necessary to hold prandial insulin, maintaining basal insulin at a lower percentage (40 %).

The prandial insulin doses are adjusted according to the results of bedside BG measurements. The supplemental (correction) fast-acting insulin analog or regular insulin is required if the patient is able and expected to eat all or most of the meals. Give regular insulin or fast-acting insulin analog before each meal following Table 31.2. If a patient is not able to eat, or is receiving enteral nutrition, give regular insulin

**Table 31.2** Supplemental doses of insulin according to BG and insulin sensitivity

BG (mg/dL)	Insulin-sensitive	Usual	Insulin-resistant
>141–180	2	4	6
181–22	4	6	8
221–260	6	8	10
261–300	8	10	12
301–350	10	12	14
351–400	12	14	16
>400	14	16	18

every 6 h or fast-acting insulin analog every 4–6 h. In patients receiving parenteral nutrition it is recommended to use continuous endovenous insulin infusion.

If fasting and premeal plasma glucose are persistently above 7.8 mmol/L (140 mg/dL) in the absence of hypoglycemia, increase insulin scale of insulin from the insulin-sensitive to the usual or from the usual to the insulin-resistant column. If a patient develops hypoglycemia (BG <3.8 mmol/L) (70 mg/dL), acts in the opposite way, decreasing regular insulin or fast-acting insulin analog from the insulin-resistant to the usual column or from the usual to the insulin-sensitive column.

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## Key Points to Diagnosis

DKA is characterized by the following:

- Hyperglycemia with blood glucose usually >300 mg/dL
- Ketonemia with total ketones in serum >3 mmol/L
- Acidosis with blood pH <7.3 or serum bicarbonate >15 meq/L
- Hyperosmolar dehydration with serum osmolality >320 mmol/L

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## Pathogenesis

The events that results in DKA are described in Fig. 32.1. The basic metabolic derangements in DKA arise secondary to a relative lack of insulin and excess in insulin counter-regulatory hormones: glucagon, catecholamines, cortisol, and growth hormone. Even in the absence of changes in insulin administration, the counter-regulatory hormones are elevated during times of stress and may outweigh the effects of insulin. This leads to catabolic disturbances in the metabolism of carbohydrates, protein, and fat, which collectively

culminate in two cardinal features of diabetic ketacidosis, hyperglycemia and ketogenesis.

Hyperglycemia develops as a result of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues. Transient insulin resistance occurs due to hormone imbalance as well as elevated free fatty acids concentrations [4]. The combination of insulin deficiency and increased counter-regulatory hormones in DKA leads to the release of free fatty acids into the circulation from adipose tissue and to unrestrained hepatic fatty acid oxidation in the liver to ketone bodies, with resulting ketonemia and acidosis.

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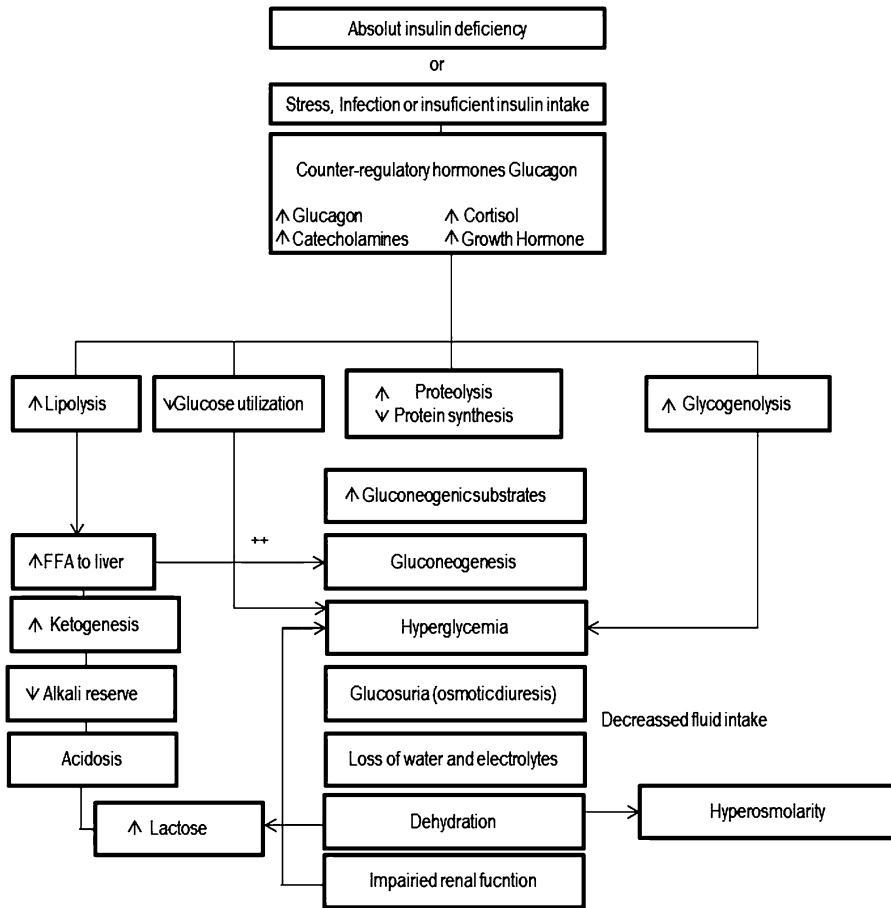
## Clinical Manifestations

The clinical manifestations of DKA include the following:

- Signs of dehydration: delayed capillary refill, postural changes of blood pressure and pulse, dry mucous membranes.
- Signs of acidosis: deep-sighing respirations (Kussmaul) in attempt to blow off carbon dioxide, shortness of breath, chest pain due to accessory muscle exhaustion.
- Results of osmotic diuresis and vomiting, dehydration, and hyperosmolality: abdominal pain mimicking pancreatitis or an acute surgical abdomen.
- Results of counter-regulatory hormone release: elevated leukocyte count to 15,000–20,000/mm<sup>3</sup>.

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**Fig. 32.1** Clinical manifestations

- Signs of hyperosmolality: progressive obtundation and loss of consciousness related to the degree of evolving hyperosmolality.

In DKA, metabolic decompensation usually develops over a period of hours to a few days. Patients with DKA classically present with lethargy and a characteristic hyperventilation pattern with deep slow breaths (Kussmaul respirations) associated with the fruity odor of acetone. They complain of nausea and vomiting, and abdominal pain is somewhat less frequent. The abdominal pain can be quite severe and may be associated with distention, ileus, and tenderness without rebound but usually resolves relatively quickly with therapy unless there is underlying abdominal pathology. Most patients are normotensive, tachycardic, and tachypneic and have signs of mild to moderate dehydration. Hypothermia has

been described in DKA, and patients with underlying infection might not manifest fever. Patients with DKA can have stupor and obvious profound dehydration, and they often demonstrate focal neurologic deficits such as Babinski reflexes, asymmetrical reflexes, cranial nerve findings, paresis, fasciculations, and aphasia [1].

### Laboratory Test Results and Differential Diagnosis

Laboratory tests that are routinely monitored in DKA include hemoglobin, white blood cell and differential count, glucose, electrolytes, arterial blood gases, ketones, blood urea nitrogen (BUN), and creatinine. The severity of DKA is classified as mild, moderate, or severe

**Table 32.1** Typical laboratory findings in DKA

	Average	Range
Plasma glucose	600 mg/dL	200–2,000 mg/dL
Plasma B-hydroxybutyrate	14 mmol/L	4–20 mmol/L
Plasma HCO <sub>3</sub>	10 mEq/L	4–18 mEq/L
Blood pH	7.15	6.80–7.30
<i>P</i> <sub>CO<sub>2</sub></sub>	20 mmHg	14–30 mmHg
Plasma anion gap (Na-[Cl+HCO <sub>3</sub> ])	29	16–35 mEq/L

based on the severity of metabolic acidosis (blood pH, bicarbonate, and ketones) and the presence of altered mental status [4].

Acidosis is always present in DKA, and the serum HCO<sub>3</sub> concentration is usually less than 10 mEq/L. The acidosis is due to production and accumulation of ketones in the serum. Three ketones are produced in DKA: two ketoacids ( $\beta$ -hydroxybutyrate and acetoacetate) and the neutral ketone acetone. Ketones can be detected in serum and urine using the nitroprusside reaction on diagnostic strips for use at the patient's bedside or in the clinical laboratory. This test detects acetoacetate more effectively than acetone and does not detect an increased concentration of  $\beta$ -hydroxybutyrate. Particularly in severe DKA,  $\beta$ -hydroxybutyrate is the predominant ketone, and it is possible although unusual to have a negative serum nitroprusside reaction in the presence of severe ketosis. However, under these circumstances the serum HCO<sub>3</sub> is still markedly reduced and the anion gap is increased, indicating metabolic acidosis. The urinary  $\beta$ -hydroxybutyrate can be measured at many centers and commercially but is not usually readily available.

The anion gap is a readily available index for unmeasured anions in the blood (normal <14 mEq/L): Anion gap = sodium – (chloride + bicarbonate).

Most patients with DKA present with an anion gap greater than 20 mEq/L, and some present with a gap greater than 40 mEq/L. However, occasional patients have a hyperchloremic metabolic acidosis without a significant anion gap [5].

Patients with DKA almost invariably have large amounts of ketones in their urine. The serum glucose in DKA is usually in the 500 mg/dL range. However, an entity known as euglycemic DKA has been described, particularly in the

presence of decreased oral intake or in pregnancy, in which the serum glucose is normal or near normal but the patient requires insulin therapy for the clearance of ketoacidosis [6]. The arterial pH is commonly less than 7.3 and can be as low as 6.5. There is partial respiratory compensation with hypocarbia. Patients are often mildly hyperosmolar, although osmolalities greater than 330 mOsm/kg are unusual without mental status changes (Table 32.1).

## Differential Diagnosis

The following causes of metabolic acidosis need to be considered in the differential diagnosis of DKA.

Lactic acidosis is the most common cause of metabolic acidosis in hospitalized patients and can be seen in patients with uncomplicated diabetes as well as those with DKA. Lactic acidosis usually occurs in the setting of decreased tissue oxygen delivery, resulting in the nonoxidative metabolism of glucose to lactic acid. Lactic acidosis complicates other primary metabolic acidoses as a consequence of dehydration or shock, and assessing its relative contribution can be difficult. The presentation is similar to that of DKA. In pure lactic acidosis, the serum glucose and ketones should be normal and the serum lactate concentration should be greater than 5 mm. The therapy of lactic acidosis is directed at the underlying cause and optimizing tissue perfusion [7].

Starvation ketosis is caused by inadequate carbohydrate availability, resulting in physiologically lipolysis and ketone production to provide fuel substrates for muscle. The blood glucose is usually normal. The urine can have large

amounts of ketones, but the blood rarely does. Arterial pH is normal, and the anion gap is at most mildly elevated.

Alcoholic ketoacidosis is a more severe form of starvation ketosis wherein the appropriate ketogenic response to poor carbohydrate intake is increased through as yet poorly defined effects of alcohol on the liver. Classically, these patients are long-standing alcoholics for whom ethanol has been the main caloric source for days to weeks. The ketoacidosis occurs when for some reason alcohol and caloric intake decreases. In isolated alcoholic ketoacidosis, the metabolic acidosis is usually mild to moderate. The anion gap is elevated. Serum and urine ketones are always present. However, alcoholic ketoacidosis produces an even higher ratio of  $\beta$ -hydroxybutyrate to acetoacetate than DKA does, and negative or weakly positive nitroprusside reactions are common. Respiratory alkalosis associated with delirium tremens, agitation, or pulmonary processes often normalizes the pH but should be evident with careful analysis of acid–base status. Usually, the patient is normoglycemic or hypoglycemic, although mild hyperglycemia is occasionally present. Patients who are significantly hyperglycemic should be treated as if they have DKA. The therapy of alcoholic ketoacidosis consists of thiamine, carbohydrates, fluids, and electrolytes, with special attention to the more severe consequences of alcohol toxicity, alcohol withdrawal, and chronic malnutrition [8].

Uremic acidosis is characterized by extremely large elevations in the BUN (often >200 mg/dL) and creatinine (>10 mg/dL) with normoglycemia. The pH and anion gap are usually only mildly abnormal. The treatment is supportive, with careful attention to fluid and electrolytes until dialysis can be performed. Rhabdomyolysis is a cause of renal failure in which the anion gap can be significantly elevated and acidosis can be severe. There should be marked elevation of creatine phosphokinase and myoglobin. Mild rhabdomyolysis is not uncommon in DKA, but the presence of hyperglycemia and ketonemia leaves no doubt about the primary etiology of the acidosis [9].

Toxic ingestions can be differentiated from DKA by history and laboratory investigation.

Salicylate intoxication produces an anion gap metabolic acidosis usually with a respiratory alkalosis. The plasma glucose is normal or low, the osmolality is normal, ketones are negative, and salicylates can be detected in the urine or blood. Salicylates can cause a false-positive glucose determination when using the cupric sulfate method and a false-negative result when using the glucose oxidase reaction detection of ketoacids [10].

When DKA is considered, the diagnosis can be made quickly with routine laboratory tests. Blood and urine glucose and ketones can be obtained in minutes with glucose oxidase-impregnated strips and the nitroprusside reaction, respectively.

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## Osmolality

The increase in osmolality (mOsm/L) that occurs in DKA must be differentiated from the increase in osmolality seen in hyperosmolar-hyperglycemic nonketotic (diabetic) coma (HHNC). The osmolality can be estimated using the following formula:  $\text{Osmolality} = (2 \times \text{sodium}) + (\text{glucose}/18)$ .

Patients with DKA rarely present with hyperosmolality and coma. In HHNC, the osmolality is generally greater than 350 mOsm/L and can exceed 400 mOsm/L. The serum sodium and potassium can be high, normal, or low and do not reflect total-body levels, which are uniformly depleted. The glucose is usually greater than 600 mg/dL, and levels higher than 1,000 mg/dL are quite common. In pure HHNC, there is not a significant metabolic acidosis or anion gap.

Patients often present with combinations of the preceding findings. HHNC can involve mild to moderate ketonemia and acidosis. Alcoholic ketoacidosis can contribute to either DKA or HHNC. Lactic acidosis is common in severe DKA and HHNC.

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## Present Therapy [11]

The general approach is to provide necessary fluids to restore the circulation, treat insulin deficiency with continuous insulin, treat electrolyte



disturbances, observe the patient closely and carefully, and search for underlying causes of metabolic disturbances.

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## Fluids

The primary goal in the initial management of DKA is to restore intravascular volume and improve tissue perfusion, and the secondary goal is to maintain a brisk diuresis. This will decrease insulin counter-regulatory hormones levels and glucose concentration [1]. Fluid replacement alone may decrease serum glucose concentration by as much as 23 % through increased renal perfusion and loss of glucose in the urine [1, 12]. Initial intravenous fluids should be given rapidly to achieve hemodynamic stability, then decreased to rate that allows for replacement of the total deficit over a 24-h period. The total body water deficit (TBW) in these patients is usually 5–10 L. The total body water deficit may be calculated by the formula:  $TBW \text{ deficit (L)} = 0.6 \times wt \text{ (kg)} + [1 - 140 / \text{serum sodium}]$ . The goal in fluid administration is to replace approximately 50 % of TBW deficit in the first 8 h and the remainder in the subsequent 16 h. The initial fluid of choice is normal saline (0.9 % sodium chloride) with 1 or 2 L administered in the first hour. The subsequent choice for fluid replacement depends on the patient's hydration status, serum electrolytes levels, and urinary output [11]. One approach suggest an infusion rate of 0.9 % NaCl 500 mL/h until hemodynamically stable. Then the rate is decreased to 250 mL/h and can be switched to half normal saline to replace the large free water deficit [1].

When the blood glucose level falls below 250 mg/dL, a solution of 5 % dextrose should be added to the intravenous fluid. This allows for continued administration of insulin to treat the ketosis and acidosis without causing hypoglycemia. The serum glucose should be maintained between 150 and 200 mg/dL until the ketoacidosis has resolved. Dextrose administration may be increased to 10 or 20 % if glucose levels remain below 100 mg/dL.

Special care should be taken to avoid overhydration in children, patients with cardiac or renal compromise, and elders with DKA. The

lung sounds and oxygenation should be assessed frequently. In children, mental status may be the first sign of cerebral edema [11].

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## Insulin

Insulin therapy will improve the hyperglycemia, ketosis and acidosis that occur in DKA. In the past, high doses of insulin (upward of 50 U/h) were favored. In later studies, low-dose insulin therapy (0.1 U/kg per hour) has been shown to be as effective as higher doses in producing a decrease in serum glucose and clearance of ketones. Furthermore, low-dose therapy results in a reduction in the major morbidity of intensive insulin therapy: hypoglycemia and hypokalemia.

Studies have also shown that intravenous insulin is significantly more effective than intramuscular or subcutaneous insulin in lowering the ketone body concentration over the first 2 h of therapy. The subcutaneous route is probably inappropriate for the critically ill patient because of the possibility of tissue hypoperfusion and slower kinetics of absorption; however, a study has documented that subcutaneous rapid-acting insulin analogue administered every 1–2 h was as safe and effective as intravenous regular insulin in the treatment of patients with uncomplicated DKA [13]. Numerous studies attest to the efficacy of intramuscular therapy in severe DKA. When there is insufficient nursing monitoring or intravenous access to allow safe intravenous administration, intramuscular therapy would be the route of choice.

Lastly, it has been shown that a 10-U intravenous insulin priming dose when insulin therapy is started significantly improves the glycemic response to the first hour of therapy. The rationale is to saturate insulin receptors fully before beginning continuous therapy and to avoid the lag time necessary to achieve steady-state insulin levels. Because insulin adsorbs to intravenous tubing, 50 mL of the infusion should be run through the pump before beginning the infusion [11].

In the rare instances in which the glucose does not decrease at least 10 % or 50 mg/dL in an hour, the insulin infusion rate should be increased by

50–100 % and a second bolus of intravenous insulin should be administered. As the glucose level decreases, it is usually necessary to decrease the rate of infusion. After the glucose reaches approximately 250 mg/dL, it is prudent to decrease the insulin infusion rate and administer dextrose. It usually takes an additional 12–24 h to clear ketones from the circulation after hyperglycemia is controlled. With resolution of ketosis, the rate of infusion approaches the physiologic range of 0.3–0.5 U/kg per day. Criteria for the resolution of DKA includes glucose less than 200 mg/dL, serum bicarbonate at least 18 mmol/L, and a venous pH greater than 7.3 [11].

When the decision is made to feed the patient, the patient should be switched from intravenous or intramuscular therapy to subcutaneous therapy. Subcutaneous insulin should be administered before a meal and the insulin drip discontinued approximately 2 h later. The glucose should be checked in 2 h and at least every 4 h subsequently until a relatively stable insulin regimen is determined. Early conversion to oral feeding and subcutaneous insulin therapy is associated with a shorter hospital stay.

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## Potassium

Potassium is the major electrolyte lost in DKA, losses during the development of DKA are usually quite high (3–10 mEq/kg) and are mediated by shifts to the extracellular space secondary to acidosis and protein catabolism compounded by hyperaldosteronism and osmotic diuresis. Although most patients with DKA have normal or even high serum potassium at presentation, the initial therapy with fluids and insulin causes it to fall.

Approach has been to monitor the electrocardiogram (ECG) for signs of hyperkalemia (peaked T wave, QRS widening) initially and to administer potassium if these are absent and the serum potassium is less than 5.5 mEq/L. If the patient is oliguric, do not administer potassium unless the serum concentration is less than 4 mEq/L or there are ECG signs of hypokalemia (U wave), and even then potassium is administered with extreme caution. With therapy of

DKA, the potassium level always falls, usually reaching a nadir after several hours. It is usually to replace potassium at 10–20 mEq/h (70 % as potassium chloride and 30 % as potassium phosphate), monitor serum levels at least every 2 h initially, and follow ECG morphology. Occasionally, patients with DKA who have had protracted courses that include vomiting, hypokalemia, and acidosis require 40–60 mEq/h by central line to prevent further decreases in the serum potassium.

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## Phosphate

Phosphate replacement has no benefit for most patients with DKA. Although patients usually present with elevated serum phosphate, the serum level declines with therapy. In certain groups of patients, phosphate replacement may be indicated to avoid cardiac dysfunction, skeletal muscle weakness, and respiratory depression [11]. These include patients with cardiac dysfunction, anemia, respiratory depression, and those with serum phosphate level less than 1.0 g/dL [11]. Hypophosphatemia causes the depletion of 2,3-diphosphoglycerate (2,3-GPD), resulting in a left shift of the oxyhemoglobin curve, resulting in decreased tissue oxygenation [14]. When phosphate is indicated, 20–30 mEq/L potassium phosphate can be added to fluids [11] replacement of phosphate in patients with levels less than 1.0 g/dL is indicated and supported by randomized controlled trials with adequate power [15].

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## Bicarbonate

Serum bicarbonate is always low in DKA, but a true deficit is not present because the ketoacid and lactate anions are metabolized to bicarbonate during therapy. The use of bicarbonate for managing DKA is not well supported in the literature [15]. Studies have shown no benefit of bicarbonate therapy for managing DKA, but these studies have looked at patients with serum pH ranging from 6.9 to 7.1 [16–18]. Because studies have not been done in patients with a pH less than 6.9,

some authors advocate bicarbonate therapy for patients with severe acidosis ( $\text{pH} < 6.9$ ), for patients with hemodynamic instability if the  $\text{pH}$  is less than 7.1, or in cases of hyperkalemia with ECG findings. The potential disadvantages of bicarbonate therapy include worsening hypokalemia, production of paradoxical central nervous system acidosis, worsening of intracellular acidosis owing to increased carbon dioxide production, and prolongation of ketoanion metabolism [19].

When bicarbonate is used, it should be used sparingly and considered a temporizing measure while definitive therapy with insulin and fluids is under way. Approximately 1 mEq/kg of bicarbonate is administered as a rapid infusion over 10–15 min, and further therapy is based on repeated arterial blood gases every 30–120 min. Potassium therapy should be considered before treatment with bicarbonate because transient hypokalemia is not an uncommon complication of the administration of alkali.

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## Monitoring

Patients with DKA are routinely admitted to a unit where frequent monitoring is possible, hourly glucose measurements can be obtained, there is a rapid turnaround time for laboratory services, and nurses are able to administer intravenous insulin infusions. Indication for admission to an intensive care unit include: pregnancy, hypotension refractory to initial rehydration, oliguria refractory to initial rehydration, mental obtundation, and sepsis [11]. If mental status is compromised, prophylactic intubation is considered and nasogastric suctioning is always performed because of frequent ileus and danger of aspiration. If the patient cannot void at will, bladder catheterization is necessary to follow urine output adequately. ECG monitoring is continuous, with hourly documentation of QRS intervals and T-wave morphology. Initially, serum glucose, electrolytes, BUN, creatinine, calcium, magnesium, phosphate, ketones, lactate, creatine phosphokinase, and liver function tests as well as urinalysis, ECG, upright chest radiograph, complete blood count, and arterial blood gases are

obtained. Subsequently, glucose and electrolytes are measured at least hourly; calcium, magnesium, and phosphate every 2 h; and BUN, creatinine, and ketones every 6–24 h.

It is often not necessary to monitor arterial blood gases routinely because bicarbonate and anion gap are relatively good indices of the response to therapy. Monitoring venous  $\text{pH}$  has also been shown to reflect acidemia and response to therapy adequately. Usually, frequent blood work is necessary only for the first 12 h or so. A flow sheet tabulating these findings as well as mental status, vital signs, insulin dose, fluid and electrolytes administered, and urine output allows easy analysis of response to therapy. When the acidosis begins to resolve and the response to therapy becomes predictable, it is reasonable to curtail laboratory testing. The goals should be to achieve hemodynamic stability rapidly and to correct DKA fully in 12–36 h.

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## Search for Underlying Causes

After stabilizing the patient, a careful history and physical examination and a diagnostic strategy should be aimed at determining the precipitating event. The two most common cause of DKA is noncompliance with insulin therapy and is usually easily treated, and infection, with viral syndromes, urinary tract infection, pelvic inflammatory disease, and pneumonia predominating. It is often difficult to determine initially whether the patient is infected. Fever is absent in a significant fraction of patients with diabetic emergencies. The white blood cell count is not uncommonly elevated in the range of 20,000 or higher even in the absence of infection [20]. As a result, cultures should be performed for most patients, and if there is significant concern about infection, empirical broad antibiotic coverage should be considered pending microbiologic findings.

Special consideration should be given to ruling out meningitis in the patient with altered mental status. In this regard, most would perform lumbar punctures in all patients with meningismus and in patients with disproportionate mental status changes. The relative frequency of sinus infection

(particularly with *Mucor*), foot infection, bacterial arthritis, cholecystitis, cellulitis, and necrotizing fasciitis should also be considered.

Pneumonia can be difficult to diagnose in patients with dehydration because the alveolar edema fluid that shows up as an infiltrate on chest radiographs is often not present but develops along with progressive hypoxia during hydration. To prevent this occurrence, we administer intravenous fluid judiciously to patients we suspect have pneumonia. Pancreatitis and pregnancy are common precipitants and should be especially considered when assessing the abdominal pain that is almost ubiquitous at presentation. Abdominal guarding and tenderness associated with vomiting are common, and rebound is occasionally present. These symptoms and findings usually resolve quickly with therapy in the absence of intra-abdominal pathology. The serum amylase is often elevated without pathologic significance, although lipase is usually more specific [21]. Myocardial infarction and stroke as well as thromboembolic phenomena are frequent precipitants and complications of DKA.

The more insulin resistant the patient seems to be, the more likely to find a precipitating cause. If a precipitating cause is found, treatment is essential to achieve adequate metabolic control.

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## Complications and Prognosis

It should now be possible to treat almost all cases of DKA successfully. The most common complications of DKA are related to the treatment and include hypoglycemia, hypokalemia and hyperchloremia [11]. Less common complications include cerebral edema, fluid overload, acute respiratory distress syndrome, thromboembolism, and acute gastric dilation. Some of these complications are related below:

### Hypoglycemia

Hypoglycemia may occur secondary to overzealous administration of insulin. The risk of hypoglycemia can be reduced by adding dextrose to

the intravenous fluid therapy when the blood glucose falls below 250 mg/dL. This allows the continued administration of insulin to resolve ketoacidosis while decreasing the risk of hypoglycemia [1, 11].

### Hypokalemia

Hypokalemia may develop secondary to treatment with insulin and bicarbonate [11]. The occurrence of this problem is less common with low-dose insulin regimens [19].

To avoid hypokalemia, insulin should not be administered until the serum potassium level is known, and replaced as have been discussed previously.

### Hyperglycemia

Hyperglycemia often occurs secondary to interruption or discontinuation of intravenous insulin therapy without proper administration of subcutaneous doses of insulin [11].

### Hyperchloremia

Patients may develop a nonunion gap metabolic acidosis as a result of excessive saline administration. Chloride replaces ketoanions lost as sodium and potassium salts during osmotic diuresis. These abnormalities are usually transient and clinically insignificant except in cases of acute renal failure or extreme oliguria [22].

### Cerebral Edema

Cerebral edema is a rare but frequently fatal complication of DKA that primarily occurs in pediatric patients. In a reported series 95 % of cases occurred in patients younger than 20 years, with one third occurring in patients younger than 5 years [23]. The incidence of cerebral edema in children with DKA is 0.7–1 % [11, 23, 24]. It is more common in patients with newly diagnosed

and the mortality rate according different series has varied between 24 and 90 % [24–26].

The clinical presentation of cerebral edema is characterized by deterioration in the in the level of consciousness, with lethargy, decrease in arousal, and headache [1, 11]. The timing of the development of cerebral edema is variable, with most cases occurring 4–12 h after starting treatment. There have been several case reports of cerebral edema occurring before the initiation of therapy [27].

The proposed pathophysiology of cerebral edema include : hypoxia, osmolality declines driven movement of water into the CNS when plasma osmolality declines too rapidly during the treatment of DKA, and the direct effect of insulin on plasma membrane of brain cells, which may promote cellular edema [1, 11, 27].

When cerebral edema develops, the treatment is aimed at reducing intracranial pressure. In the case reports of treatments, mannitol has been used to lower intracranial pressure, and is recommended that it be administered within 5–10 min of initial neurological deterioration for maximum effect [27]. The dose of mannitol is 1–2 g/kg over 15 min. Intracranial pressure monitoring and hypoventilation started immediately after cerebral edema is suspected have been reported to improve outcome [27–29]. The role of dexamethasone and diuretics has not been established [15, 27]. Preventive measures that might decrease the risk of cerebral edema in high risk patient are: Gradual replacement of sodium and water deficits in patients who are hyperosmolar (maximal reduction in osmolality of 3 mOsm/kg H<sub>2</sub>O per hour), avoidance of bicarbonate administration unless absolutely necessary, and addition of dextrose to the fluid therapy once blood glucose reaches 250 mg/dL [11].

## Fluid Overload

Patients with underlying cardiac disease or renal insufficiency who receive excess fluid or rapid administration of liquids may develop congestive heart failure. In these patients, monitoring of cardiac or renal status must be performed during fluid resuscitation to avoid iatrogenic fluid overload [1, 30].

## Thromboembolism

Diabetes mellitus is a hypercoagulable state. Subclinical endothelial injury, hypofibrinolysis, and platelet hyperaggregation are the main factors responsible for coagulation activation in diabetes mellitus [31]. In a DKA this hypercoagulable state is enhanced, as has been showed in a study of 34 patients with DKA, where hemostatic markers were measured during DKA and 1 week after resolution of DKA. During DKA patients were found to have coagulation system and platelet activation, endothelial injury, and a relative hypofibrinolysis [32]. Standard prophylactic low-dose heparin is certainly reasonable in patients with DKA, but currently no indication exists for full anticoagulation.

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## Future Therapies and Prevention

DKA can be prevented in many cases by better access to medical care, proper patient education and effective communication with health care provider during an intercurrent illness. Insulin omission or difficulties to deal with stressful events of life are the most common causes. Therefore, patients and family members must be educated and undergo training for intensive monitoring, ketone detection and insulin dose adjustments with supplemental short or rapid-acting insulins during intercurrent illness and the reasons to never discontinue without contacting the health care team. Adult supervision of children to insulin administration, psychological assessment, and support for patients and their family may contribute to the reduction in frequency of recurrent DKA [33].

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## Key Points

1. Perform a history and physical examination in search of a precipitating cause.
2. A patient may present with DKA with a near normal glucose. This is more common in patients who have taken insulin recently, have decreased food intake, or have impaired gluconeogenesis as can be seen in liver disease.

3. Consider other causes of anion gap metabolic acidosis.
4. Initial therapy consists of intravenous fluid administration. It is prudent to wait for adequate rehydration and serum potassium levels before starting insulin or potassium therapy.
5. Frequent monitoring of glucose and electrolytes should guide further treatment.
6. Caution should be used in fluid administration in patients with cardiovascular and renal disease.
7. If abdominal pain does not resolve with initial treatment, consider evaluation for abdominal pathology.
8. Treatment of rare complications such as cerebral edema requires further studies before the development of standards of care.

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## Clinical Presentation

The symptoms of hypoglycemia can be divided into two groups: (1) autonomic/neurogenic and (2) neuroglycopenic [4]. Autonomic symptoms are caused by activation of the sympathoadrenal system. Symptoms may be adrenergic such as palpitations and anxiety, or they may be cholinergic such as sweating or hunger. Neuroglycopenic symptoms are caused by an insufficient glucose supply to the brain leading to functional brain impairment including confusion and fatigue, loss of consciousness, and seizures [1]. Autonomic symptoms usually occur at a threshold of 60 mg/dl, whereas neuroglycopenic symptoms occur at a threshold of 50 mg/dl. Glycemic thresholds may be dynamic and if hypoglycemia is recurrent, the threshold may shift lower [5, 6].

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## Pathophysiology

In the fasting state, blood glucose is maintained by release of glucose from the liver and less so, the kidney. Glycogen stores may be depleted if the fasting state is prolonged. Counter-regulatory

measures are in place to effectively maintain a constant glucose supply to the brain. As blood glucose falls, insulin secretion is suppressed, thereby decreasing peripheral glucose disposal. This usually occurs at a threshold of ~80 mg/dl, a glucose level within normal physiological range [7]. Cessation of insulin is clearly not the only mechanism to prevent hypoglycemia [8]. Glucagon plays a very important role in preventing hypoglycemia and is considered one of the critical counter-regulatory hormones. It is released at a glucose threshold of ~65 mg/dl and stimulates both gluconeogenesis and glycogenolysis. If glucagon is deficient, epinephrine becomes a critical counter-regulatory hormone and has a glucose threshold similar to glucagon. Cortisol and growth hormone are released in response to prolonged hypoglycemia, but their role in normal physiologic circumstances is unclear. Other mechanisms to counteract hypoglycemia include glucose autoregulation which refers to the ability of glucose per se to regulate its own production independent of hormonal and neural effects [7].

In the fasting state, lipolysis occurs so that the demand for glucose is reduced, thereby preventing muscle breakdown. Lipolysis leads to an increase in free fatty acids with subsequent ketogenesis by conversion of fatty acids to beta hydroxybutyrate and acetoacetate, which can be used by the brain as an alternative fuel.

Disruption of physiological defenses may lead to hypoglycemia:

1. Inability to ingest carbohydrates
2. Excess insulin

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3. Inadequate secretion of counter-regulatory hormones
4. Excess insulin-like factors
5. Defects of the gluconeogenic or glycogenolytic pathways

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## Differential Diagnosis

The differential diagnosis of hypoglycemia depends on the general well-being of the patient—the likely causes of hypoglycemia differ significantly between the outpatient (healthy patients) setting and the inpatient setting (where patients usually have significant systemic illness). The characterization of hypoglycemic disorders by the timing of symptoms in relation to food intake does not work clinically because certain conditions may lead to hypoglycemia in both states, and sometimes it may be difficult to reliably differentiate the timing of symptoms in a given patient. Sometimes, fasting and postprandial symptoms coexist in the same patient [9]. Consequently, this classification has largely been abandoned.

In patients who seem well, endogenous hyperinsulinemic hypoglycemia is the most common cause whereas underlying systemic disease and iatrogenic factors play a bigger role in ill or medicated patients.

It is important to decide which patients to evaluate for hypoglycemia, to avoid unnecessary testing and expense. A thorough history, physical examination, and review of laboratory data are important, particularly if the patient describes symptoms that are suggestive of neuroglycopenia. Approaches may differ depending on the clinical situation, i.e., medicated, ill, and hospitalized patients versus healthy patients without significant comorbidities.

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## The Healthy Patient

### Hyperinsulinemic Hypoglycemia

Endogenous hyperinsulinemic hypoglycemia was first described at Mayo Clinic in 1926 [10]. A surgeon, with metastatic pancreatic islet cell tumor,

presented with hypoglycemic events. Extracts from the liver metastases obtained at the time of abdominal exploration led to hypoglycemia in laboratory animals. This confirmed that the tumor itself was leading to excessive insulin secretion and the clinical entity of insulinoma was established.

### Insulinoma

Insulinomas are rare islet cell tumors with an incidence of 1 in 250,000 patient-years [11]; however, insulinomas represent the most common cause of hyperinsulinemic hypoglycemia. There is a slight predominance in women and may occur in people of all ethnicities. Insulinomas are usually benign, small, solitary tumors but may be multiple in less than 10 % of cases. Ninety percent are less than 2 cm in size. Insulinomas may be sporadic or part of a genetic syndrome, such as multiple endocrine neoplasia 1 (MEN 1). Recurrence is approximately 7 % in patients without MEN 1 or malignant insulinoma [11, 12].

Insulinomas classically present with hypoglycemia in the post-absorptive state; however, hypoglycemia can also occur in the postprandial state [13, 14]. Patients often appear healthy, except for periods of neuroglycopenia. Lesions are usually identified on imaging studies and surgical enucleation or resection is the treatment of choice.

Malignant insulinomas account for 5–10 % of insulinomas [15]. Presentation is similar to that of other hypoglycemia disorders. Malignant tumors are differentiated from benign tumors based on the presence of extrapancreatic invasion and lymph node involvement. A 10-year survival rate of 29 % has been reported [15].

### Non-insulinoma Pancreatogenous Hypoglycemia (NIPHS)

NIPHS was first described in 1999 by FJ Service and colleagues at the Mayo Clinic [16]. Five adult patients were reported with hyperinsulinemic hypoglycemia in the postprandial state, not consistent with insulinoma. Histology of resected tissue typically showed pancreatic islet cell hypertrophy and nesidioblastosis. No mutation in Kir6.2 and SUR1 genes was present, which has previously been associated with familial persistent hyperinsulinemic hypoglycemia of infancy.

NIPHS is typically characterized by:

1. Hypoglycemia in the postprandial state, usually between 2 and 4 h
2. Negative imaging studies
3. Abnormal selective arterial calcium stimulation tests in those gone to surgery
4. Nesidioblastosis or occult islet tumor on histology

The mixed meal test can help confirm hypoglycemia in the postprandial state but does not establish a diagnosis. Treatment includes medical therapy or partial pancreatectomy, guided by the selective arterial calcium stimulation test.

### Hypoglycemia in Bariatric Surgery

Bariatric surgery patients may present with multiple symptoms in the postoperative period that are nonspecific and are not necessarily secondary to hypoglycemia. There seems to be a female predominance in presentation. Symptoms are frequently provoked by poor food choices. Hyperinsulinemic hypoglycemia secondary to nesidioblastosis and insulinoma has however been reported in these patients with caloric restriction unmasking symptoms [17, 18]. At Mayo Clinic, 37 patients with a history of Roux en Y gastric bypass (RYGB) were evaluated after being diagnosed with hyperinsulinemic hypoglycemia [17]. Twenty-three patients underwent pancreatic resection, with pathology showing islet cell hypertrophy similar to that seen in NIPHS. Other treatment options that have been reported include medical therapy such as calcium channel blockers, or more aggressive approaches such as tube feeding and reversal of the surgical procedure. Ninety percent of patients who have undergone extended distal pancreatectomy develop recurrence of symptoms. What is currently unknown is the incidence of nesidioblastosis and abnormal selective arterial calcium stimulation tests in asymptomatic RYGB patients. Determining the underlying etiology of nonspecific symptoms may be challenging. Despite symptoms predominating in the postprandial period, mixed meal studies are necessary to document postprandial hypoglycemia with accompanying neuroglycopenia prior to proceeding with invasive testing and treatment.

### Insulin Antibody Mediated Hypoglycemia

Insulin antibodies were previously thought to only occur in the setting of exposure to animal insulin due to high antigenicity. Insulin autoantibody hypoglycemia is a rare disorder, more commonly seen in Asians of Korean or Japanese descent [19, 20]. Patients often have a history of other autoimmune disorders. Monoclonal or polyclonal antibodies to human insulin occur even without a history of prior exposure to exogenous insulin [20]. This disorder leads to unregulated release of insulin bound to the antibodies regardless of the serum glucose. Symptoms of hypoglycemia may range from mild to severe, and can occur in both the fasting and postprandial state. Antibodies can also affect the insulin immunoassay leading to high measured insulin levels [19]. Treatment may be challenging in patients with severe hypoglycemia who do not respond to dietary and lifestyle changes.

### Drugs

Drug evaluation in the healthy patient differs from that of the ill patient. In the healthy, nondiabetic patient, the clinician should have high suspicion for factitious hypoglycemia [21–23]. This is typically seen in patients who have access to medical supplies such as health care workers or those who have sick relatives [24]. Other etiologies include accidental ingestion secondary to a dispensing error or accidental ingestion of a relative's tablets [25].

### Genetic Causation and Predisposition to Hypoglycemia

Specific gene mutations may lead to hypoglycemia at an early age. These include mutations of glucokinase gene, glutamate dehydrogenase gene and B cell sulfonylurea receptor gene. Biochemical features appear similar to other causes of hyperinsulinemia hypoglycemia.

MEN 1 is an autosomal dominant disease caused by mutations in the *MENIN* gene located in chromosome 11q13 [26, 27]. Sporadic mutations may occur in 10 % [28]. The syndrome is characterized by pituitary, parathyroid, and pancreatic disease. Lipomas, angiofibromas, and

adrenocortical tumors are also characteristic. Hypoglycemia associated with insulinomas may be the presenting symptom and usually occur at an earlier age than insulinomas in patients without MEN 1 (<40 years) [29]. Tumors may be multicentric and there is a higher rate of recurrence (21 %) compared to insulinoma patients without MEN 1 [30].

## The Ill Patient

Hypoglycemia in ill and hospitalized patients is often multifactorial. The causes include:

1. Defects in counter-regulatory hormones in the setting of systemic disease
2. Iatrogenic

Hospitalized patients are particularly at risk of hypoglycemia due to multisystem disease with higher likelihood of concomitant steroids, intravenous medications, and enteral/parenteral feeding. Examples of systemic illness leading to hypoglycemia include liver disease, malnutrition, renal failure, shock and adrenal insufficiency [31]. Iatrogenic hypoglycemia may occur when feeds or glucocorticoids are stopped in a nondiabetic treated with insulin. Hypoglycemia may also be caused by drugs apart from insulin or insulin secretagogues. Reported cases have included propoxyphene and quinine [32, 33].

Hypoglycemic episodes need to be evaluated so that the underlying etiology can be determined and further episodes prevented.

## Non-insulin Mediated Hypoglycemia

Non-islet cell tumor induced hypoglycemia is most commonly described in patients with large, slow-growing tumors particularly of mesenchymal origin [34]. Hypoglycemia may be attributed to a paraneoplastic phenomenon or may be secondary to high tumor metabolic rates. Tumors may be benign or malignant. The underlying mechanism of hypoglycemia includes tumor production of “big” IGF 2 which is incompletely processed pro-IGF 2 with insulin-like activity. Other biochemical abnormalities include low

serum growth hormone and IGF 1 due to negative feedback on the pituitary. Biochemical workup reveals a low serum glucose with suppressed insulin, proinsulin, and C-peptide, and a >25 mg/dl response in serum glucose to glucagon administration. Treatment is aimed principally at elimination of the tumor. Other medical treatments have included steroids, growth hormone, and somatostatin [35–37].

## Evaluation

It may not always be possible for the patient to obtain the necessary lab work at the time of symptoms. If the history and laboratory data are suggestive of a hypoglycemic disorder, it may be necessary to provoke the symptoms. This can be done by performing a 72-h fast if symptoms suggest a post-absorptive process and a mixed meal study if symptoms suggest a postprandial process. Figure 33.1 is a decision tree for the initial diagnosis and evaluation of a patient with hypoglycemic symptoms.

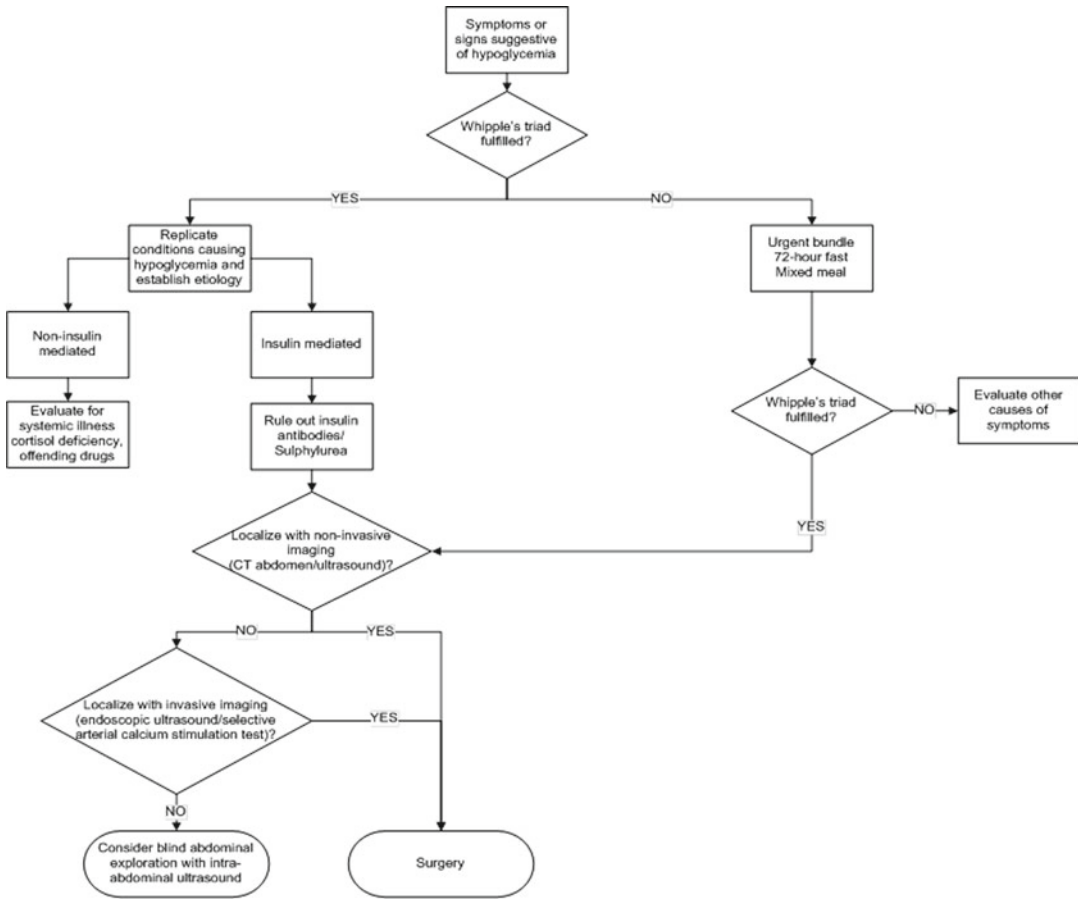
## Seventy-Two Hour Fast

The 72-h fast is prolonged withholding of food and caloric fluids until Whipple’s triad has been documented. This should be undertaken by a center that is experienced in performing the test. The fast can be initiated as an outpatient as 35 % of patients have a positive fast in the first 12 h. Those that have a negative study can be admitted to complete the fast. In a group of 170 insulinoma patients, 93 % had a positive fast by 48 h of fasting and 99 % by 72 h [15].

Criteria for ending the fast:

1. Documentation of Whipple’s triad
2. Serum glucose <55 mg/dl with previous documentation of Whipple’s triad
3. Progressive increase in beta hydroxybutyrate
4. At 72 h if no symptoms or severely depressed glucose level occurs

Ending the fast may be a difficult, especially in the setting of nonspecific symptoms with low normal serum glucose near the hypoglycemic



**Fig. 33.1** Decision tree for the diagnosis and workup of hypoglycemic disorders

threshold. Confounding this difficulty is the fact that low serum glucose may be physiological, and glucose levels in the 40–50 mg/dl range are not uncommonly seen, particularly in young lean women. A detailed history should be taken from the patient at the time of the symptoms to establish whether neuroglycopenia is occurring. Tests can include those of cognitive function, for example serial 7 s. Frequent reevaluation may be needed, including the need for bedside glucose testing if laboratory values are delayed.

### Criteria for Hyperinsulinemia

1. Plasma insulin concentrations  $\geq 3 \mu\text{U/ml}$
2. C-peptide  $\geq$  to 200 pmol/l
3. Proinsulin  $\geq$  to 5 pmol/l
4. Beta hydroxybutyrate  $< 2.7 \text{ mmol/l}$ . Hyperinsulinemia leads to a persistent suppression of beta hydroxybutyrate. A negative fast is suggestive if the beta hydroxybutyrate level is  $> 2.7 \text{ mmol/l}$  or if two consecutive values 6 h apart exceed the value at 18 h of the fast [38].
5. Response to glucagon. In patients with hyperinsulinemia, glycogen stores are sufficient; therefore a generous serum glucose response should occur in response to glucagon. An increment of 25 mg/dl from the terminal fasting glucose should be seen in patients with hyperinsulinemia.
6. Measurement of sulfonylureas and meglitinides using liquid chromatographic tandem mass spectrography. The evaluation will otherwise appear identical to an insulinoma.
7. Absence of insulin antibodies.

The interpretation of insulin, C-peptide, and proinsulin concentrations during the prolonged supervised fast depends on the concomitant plasma glucose concentration. The normal overnight fasting ranges for these polypeptides do not apply when the plasma glucose is 50–55 mg/dl or lower.

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### Mixed Meal

Standards have not been established for the mixed meal study. The study is performed in patients with symptoms of postprandial hypoglycemia. The test is performed over 5 h after the patient ingests a meal that typically produces the symptoms. A positive result includes symptoms suggestive of neuroglycopenia in the setting of a glucose  $\leq 50$  mg/dl. It is important to note that a positive test does not provide a diagnosis, rather confirmation of Whipple's triad in the postprandial state. If insulinoma is still suspected in a patient with positive mixed meal study, the 72-h fast may be performed. If the 72-h fast is negative, NIPHS should be suspected [16].

### Selective Arterial Calcium Stimulation

Selective arterial calcium stimulation may be used as both a diagnostic and localization test.

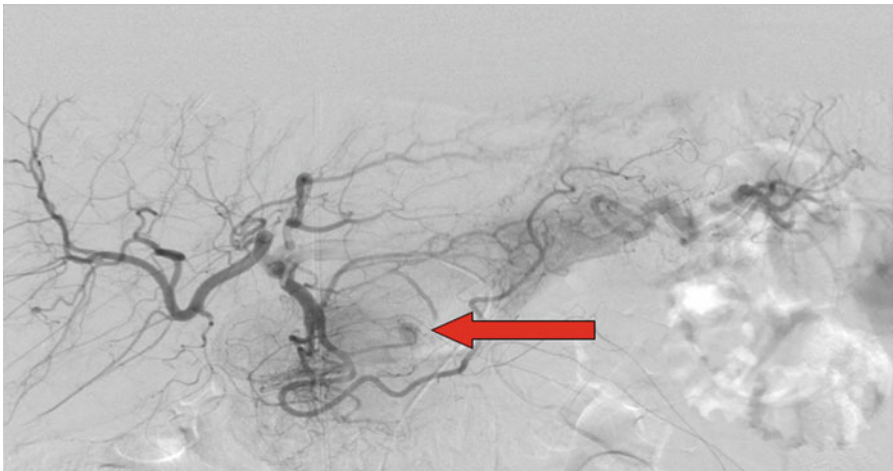
It is indicated in patients suspected of having an insulinoma with absence of lesion or multiple lesions on imaging, or hypoglycemia secondary to NIPHS. This technique is highly sensitive, previously reported at 96 % [39]; but maybe dependent on operator experience. The procedure includes puncture of the femoral vein with catheterization of the right hepatic vein via the inferior vena cava. Calcium gluconate is selectively injected into the gastroduodenal artery, superior mesenteric artery, and splenic artery. A rise in hepatic vein insulin two- to threefold at 20, 40, and 60 s after injection of calcium will localize the excess insulin secretion to head of the pancreas (gastroduodenal artery), the uncinate (superior mesenteric artery), and the body or tail (splenic artery) (Fig. 33.2 and Table 33.1 showing arteriogram and corresponding venous insulin levels in a 53-year-old female with hyperinsulinemic hypoglycemia).

Selective arterial calcium stimulation test may be used as a diagnostic tool in patients with renal failure, when beta cell polypeptides are unreliable [40].

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### Localization

Once hyperinsulinemic hypoglycemia is confirmed, the next step is to localize the lesion. Imaging techniques are successful in locating



**Fig. 33.2** A 53-year-old female with hyperinsulinemic hypoglycemia. Arteriogram after calcium gluconate infusion into the superior mesenteric artery, gastroduodenal artery, and splenic artery reveals a vascular “blush” in the gastroduodenal artery

**Table 33.1** Calcium stimulated hepatic venous sampling showing a sixfold increase in venous insulin levels in the arterial domain of the gastroduodenal artery at 40 s, corresponding to the abnormal arteriogram

Venous insulin (mcIU/ml)	Superior mesenteric artery	Gastroduodenal artery	Splenic artery
Systemic insulin	20.1	9.7	7.3
Hepatic (baseline)	14	10	7.7
Insulin 20 s	13.8	30.7	8.2
Insulin 40 s	15.5	64.6	8.5
Insulin 60 s	12.7	44	7.8

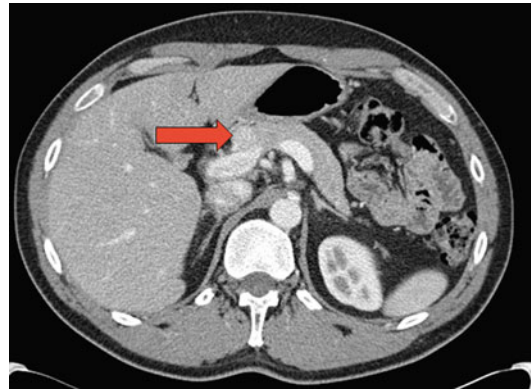
Stimulated insulin levels in the superior mesenteric and splenic arteries remain flat

insulinomas for majority of cases due to the hypervascularity of the lesions. Imaging not only localizes the primary tumor, it also allows for evaluation of metastatic lesions. Localization is important as it will prevent morbidity associated with extensive abdominal explorations and possible need for repeat surgeries. Surgical cure may depend on accurate localization of the tumor.

Transabdominal ultrasonography (TUS), endoscopic ultrasound (EUS), intraoperative ultrasound (IOUS), computed tomography (CT), and arteriography have been used. Decision about which study to perform will depend on center experience and expertise.

### Noninvasive Techniques

The advantage of noninvasive techniques is lower expense and fewer complications. TUS has a sensitivity of 9–67 % and CT scan 71–82 % [41, 42]. Large body habitus may reduce sensitivity. Imaging characteristics of CT typically involve enhancing, vascular lesions visualized during both arterial and portal venous phases, although smaller lesions are better seen during the arterial phase (Figs. 33.3 and 33.4). Lesions do not classically alter of the natural contour of the pancreas. The presence of calcification is usually a sign of malignancy as well as invasion and necrosis [41].



**Fig. 33.3** Contrast-enhanced computed tomography of the abdomen including triphasic imaging through the pancreas of a 38-year-old male with hyperinsulinemic hypoglycemia. A subtle, rounded, 1.8-cm nodule in the neck of the pancreas slightly enhances on the late arterial phase, concerning for an insulinoma



**Fig. 33.4** A 48-year-old female with hyperinsulinemic hypoglycemia. Contrast-enhanced computed tomography of the abdomen including triphasic imaging through the pancreas reveals a 7-mm nodule in the posterior tail of the pancreas, concerning for an insulinoma

### Invasive Techniques

EUS has a reported sensitivity greater than 90 % [43, 44] and is indicated if localization fails by noninvasive techniques. Intraoperative ultrasound has a sensitivity of 75–100 % if performed by experienced providers and is particularly helpful in detecting lesions in MEN 1. Both

techniques are useful in mapping anatomy with respect to the pancreatic duct and blood vessels [45]. Arteriography is now only limited to the selective arterial calcium stimulation test in our practice.

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## Treatment

### Insulinomas

Localization and resection is the treatment of choice, preserving both endocrine and exocrine function if possible. Successful removal of the insulinoma will lead to a normal life expectancy for the patient. Very deep lesions may require segmental resection, but solitary, superficial lesions may only require enucleation. More extensive resection is required if there is concern for malignancy. Insulinomas associated with MEN 1 may require a distal subtotal pancreatectomy for lesions in the body or tail of the pancreas. Lesions in the head of the pancreas can either be enucleated or treated with ethanol injection which will be discussed below.

### NIPHS

NIPHS is initially treated with dietary and medical therapy. If patients continue to have intolerable symptoms despite these measures, surgical resection is indicated. This involves localization of the region of beta cell hyperfunction by selective arterial calcium stimulation. Although thought to be a diffuse process, insulin response to calcium injection often localizes to one arterial domain. Once identified, partial pancreatectomy is recommended.

### Non Islet Cell Tumor Hypoglycemia

Treatment of the underlying tumor seems most effective. Other successful medical therapies have included growth hormone and glucocorticoids.

### Iatrogenic

Offending drugs should be eliminated. Interruptions in enteral/parenteral feeds and glucocorticoids should be minimized if insulin is being administered for hyperglycemia. Hypoglycemia in the setting of underlying systemic disease should be identified and prevented.

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### Future Therapies

Patients who are poor surgical candidates or who do not wish to pursue surgery have historically been treated with medical therapy. Diazoxide has been most effective, but side effects and tachyphylaxis are not uncommon. Frequent small meals can help prevent symptoms of neuroglycopenia; however, compliance is poor due to weight gain. Ethanol injection into the tumors is a novel therapy that may be appropriate in patients who are poor surgical candidates. Levy and colleagues [46] at Mayo Clinic reported 8 patients with insulinoma, 7 sporadic, 1 with MEN1, who were treated with ethanol therapy. Patients were unable to undergo surgery due to requirement of extensive surgery, significant comorbidities, incomplete resection, frozen abdomen, or history of intraoperative bleeding during attempted resection. Four patients were treated, or had recently been treated with diazoxide, octreotide, olanzapine, prednisone, acarbose, or exenitide. Size of insulinomas ranged 9–23 mm. Injection was guided by EUS ( $n=5$ ) and IOUS ( $n=3$ ). Fourteen treatment sessions were performed. Ethanol volume was 0.8 ml (0.12–3) and 1.1 ml (0.7–1.5) for EUS and IOUS guided procedures respectively. No complications occurred during EUS. During IOUS, 1 patient developed peritumoral bleeding. A second patient developed a 1.7 cm fluid collection and 8 cm pseudocyst. A third patient was hospitalized with pancreatitis and peripancreatic fluid collection. No surgical intervention was performed in either patient. Mean follow up was 13 months. Five patients no longer had symptoms of hypoglycemia, 3 patients felt significant improvement of

their symptoms. Three patients required the addition of low-dose diazoxide in conjunction with the ethanol therapy to control hypoglycemia.

## Conclusion

Hypoglycemia may be life threatening and necessary evaluation should ensue if neuroglycopenia is suspected. Further diagnostic tests should be performed including the 72-h fast or mixed meal study to document Whipple's triad. Hyperinsulinemic hypoglycemia most commonly occurs in otherwise healthy patients, with insulinoma predominating. NIPHS is a relatively newer clinical entity that has also been seen in bariatric surgery patients. In contrast, ill patients may have hypoglycemia that is multifactorial including underlying systemic disease and iatrogenic factors. In both healthy and ill patients, drug induced hypoglycemia should be excluded. Treatment of hypoglycemia includes relief of neuroglycopenia. Other treatments should be directed at the underlying disorder.

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## Introduction

It is well established that intensive glucose control in patients with type 1 and type 2 diabetes reduces microvascular complications in the long term [1, 2]. However, this continues to be achieved at the expense of increased risk of hypoglycaemia. Current insulin secretagogues or conventional subcutaneous insulin delivery cannot replace the physiology of the  $\beta$  cell. As a result, insulin concentrations are often inappropriately raised. Hypoglycaemia thus remains a common side effect of diabetes treatment and one that is most feared by patients. Hypoglycaemia is not only an unpleasant experience but is associated with potentially serious physical and psychological consequences. It remains the main limiting factor in achieving optimal glucose control in patients with insulin or sulphonylurea treated diabetes [3]. Furthermore, data from recent trials have suggested that hypoglycaemia is associated with increased mortality [4, 5].

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## Definition

A clinical definition based on Whipple's triad (decreased blood glucose, symptoms compatible with hypoglycaemia which resolves with consumption of carbohydrate) remains relevant in day-to-day practice [6]. Hypoglycaemia can be further classified according to severity and the broad definitions have been widely adopted both clinically and in research settings. A mild/moderate episode is one in which the person is able to self-treat. A severe hypoglycaemic episode is where the person requires external assistance to recover. It has been more difficult to agree biochemical thresholds for hypoglycaemia despite recent attempts [7]. The varying definitions and self-reported nature of hypoglycaemic episodes have made it difficult to compare incidence between studies.

Based on observational data, it is estimated that most patients with type 1 diabetes will experience 1–2 mild hypoglycaemic episodes per week and 1–2 episodes of severe hypoglycaemia per year [8]. One in ten severe episodes will involve contact with the emergency services. The risk of hypoglycaemia is lower in type 2 diabetes compared with type 1 diabetes, because when endogenous insulin secretion is relatively intact, counterregulatory responses are preserved (see below). A prospective study of patients attending hospital clinics in the UK has estimated the risk of severe hypoglycaemia at around 0.1 episodes per patient per year in patients taking sulphonylureas [9]. Rates of severe hypoglycaemia were no

higher in patients with Type 2 diabetes recently started on insulin compared to those taking sulphonylureas. The incidence of hypoglycaemia is highly skewed, with a large number of events concentrated in a small proportion of at risk patients.

## **Morbidity and Mortality Associated with Hypoglycaemia**

### **Acute Effects of Hypoglycaemia**

Even mild hypoglycaemia which leads to symptoms and cognitive side effects impacts the lives of patients. It is been estimated some individuals take around half a day to recover from a non-severe episode [10]. Patients who have suffered nocturnal hypoglycaemia are less able to function normally the next day [10]. Severe hypoglycaemia can lead to loss of consciousness and seizures resulting in physical injuries [11] and in the elderly, hypoglycaemic events are associated with increased fall-related fractures [12]. Road traffic accidents as a result of hypoglycaemia are relatively uncommon but consequences can be lethal [11].

The number of deaths directly attributed to hypoglycaemia is difficult to estimate. Hypoglycaemia is often unrecognised and post-mortem changes in blood glucose can prevent confirmation of a suspected hypoglycaemic death. In young adults with type 1 diabetes, it is been estimated the proportion of deaths caused by hypoglycaemia is between 7 and 10 % [13, 14], slightly lower than that associated with ketoacidosis. Death due to acute hypoglycaemia may be preceded by permanent brain damage, myocardial or cerebral infarction, or related to secondary complications due to convulsion and injury. Hypoglycaemia has also been linked to the “dead-in-bed syndrome”. This describes a scenario in type 1 diabetic patients with no macrovascular complications, who go to bed apparently well and are found dead in an undisturbed bed in the next morning [15]. Commonly, cause of death cannot be established at autopsy and our group have hypothesised that nocturnal hypoglycaemia, in vulnerable individuals might precipitate fatal arrhythmias [16].

### **Long Term Effects of Hypoglycaemia**

The long term emotional consequences of hypoglycaemia can be devastating. The loss of control and independence may lead to constant fear of a hypoglycaemic episode. Many patients rate fear of hypoglycaemia as much as developing long term complications. Risk of hypoglycaemia presents a major barrier to some in maintaining tight glycaemic control while individuals prone to recurrent hypoglycaemia are a constant source of anxiety to family and carers [17].

There is ongoing debate as to whether repeated episodes of severe hypoglycaemia can cause cumulative deterioration in cognitive function. Earlier retrospective, cross-sectional studies suggested that recurrent severe hypoglycaemia led to moderate cognitive decrements [18]. However prospective data from the Diabetes Control and Complications trial (DCCT) showed no apparent deterioration in cognitive function in patients with recurrent hypoglycaemia over 18 years [19]. Several large scale studies have highlighted a possible association between hypoglycaemia and dementia in elderly patients with type 2 diabetes [20]. However, it is difficult to determine the direction of causality, as cognitively impaired patients are also more vulnerable to hypoglycaemia.

A further controversy has recently emerged as to whether hypoglycaemia can increase mortality in individuals with Type 2 diabetes. Three large scale randomised controlled trials have recently explored the effect of intensive glycaemic control on macrovascular disease, in established type 2 diabetic patients with cardiovascular risk. Intensive control increased the risk of hypoglycaemia but failed to reduce macrovascular events significantly in two studies [21, 22] and in the ACCORD study appeared to increase mortality [4]. Post hoc analyses reported a history of preceding hypoglycaemia as a strong independent predictor of death [22]. Overall mortality was twofold to threefold higher and cardiovascular mortality, threefold higher in those who have experienced hypoglycaemia [5, 23]. Interestingly, during trials of intensive insulin therapy in

non-diabetic critically ill patients, the risk of death in patients who experienced hypoglycaemia was twofold higher compared to those without [24]. In the absence of a direct link between hypoglycaemia and death it is not possible to confirm causality. The association might also be the result of confounding, in that patients experiencing hypoglycaemia are more likely to die [5]. However, hypoglycaemia generates pathophysiological changes particularly those due to activation of the sympathoadrenal system which have the potential to aggravate ischemic heart disease. Experimental studies have shown that hypoglycaemia produces abnormalities in cardiac repolarization, reduces myocardial perfusion and exerts acute pro-inflammatory and pro-thrombotic effects [25]. Thus, although the precise morbid effects of hypoglycaemia are still to be established, there is a clinical imperative in minimising its frequency and effects.

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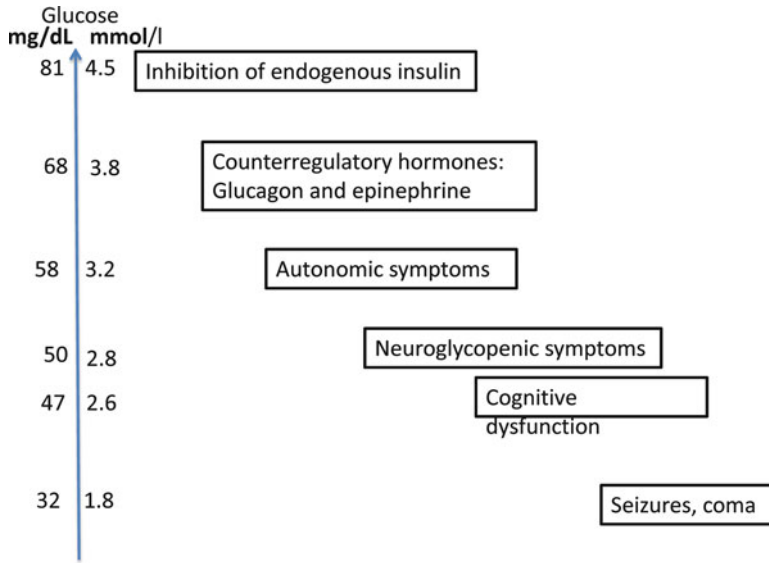
## Presentation

A complex hierarchy of autonomic and neuroendocrine defences ensures that the glucose supply to the brain (its prime metabolic substrate) is maintained. In a non-diabetic individual, pancreatic insulin secretion is suppressed when glucose falls to around 80 mg/dl (4.5 mmol/l) [26]. At lower glucose concentrations, of around 65–70 mg/d (3.6–3.9 mmol/l), the counterregulatory hormones, glucagon and catecholamines are released which stimulates glycogenolysis and gluconeogenesis, while reducing peripheral glucose uptake. However, in those with established type 1 diabetes (who have lost the ability to regulate release of insulin from the  $\beta$  cells) glucagon release from  $\alpha$  cells, which is mediated by adjacent  $\beta$  cells, is progressively impaired [27]. Thus within a few years of diagnosis, individuals with Type 1 diabetes are particularly dependent on the catecholamine response as a primary defence against hypoglycaemia. During prolonged hypoglycaemia, release of cortisol and growth hormone may also contribute to glucose recovery, although release of these hormones during hypoglycaemia is also diminished with increased duration of disease [28] (Fig. 34.1).

Activation of the sympathetic neural system also contributes to the generation of peripheral symptomatic responses to hypoglycaemia. Early after diagnosis, adults characteristically experience tremor, palpitations, anxiety, sweating, hunger, paraesthesiae at glucose concentrations of around 65 mg/dl (3.5 mmol/l). These “autonomic” symptoms alert individuals and prompt them to consume carbohydrate. Additional symptoms (“neuroglycopenic”) generally develop at 50–54 mg/dl (2.8–3.0 mmol/l). These include confusion, drowsiness, odd behaviour, speech difficulties and in-coordination. Elderly patients may experience an additional group of neurological symptoms that can be confused for a cerebrovascular event [29]. Diagnosis is usually straightforward where a concomitant blood glucose is measured at the time of presentation. However, patients often treat themselves when symptomatic before checking their blood glucose.

If glucose levels fall to 35 mg/dl (2 mmol/l) or below, this usually produces profound neurological impairment which may include focal and generalised seizures. Seizures are often mistaken for idiopathic epilepsy (and rarely, vice versa) since EEG changes can be similar. In rare cases where blood glucose is less than <20 mg/dl (1.0 mmol/l) for a protracted period, irreversible neuronal damage can occur. Magnetic resonance imaging typically shows lesions in the cerebral cortex and hippocampus with sparing of hindbrain structures. Some patients may survive but remain in a persistent vegetative state [30].

Symptoms of hypoglycaemia can vary between and even within individuals. Factors which may modulate symptoms and awareness include sex, age, diurnal effects, prevalent glycaemic control, previous hypoglycaemic episodes. In adults with type 1 diabetes, symptoms are often reset to develop at lower glucose thresholds compared to non-diabetic individuals, particularly in those with tight glycaemic control or long duration diabetes. However, in those with type 2 diabetes, thresholds are often set at higher glucose levels, even on occasions in the normal range (above 70 mg/dl or 4 mmol/l) [31].



**Fig. 34.1** Thresholds to hormonal, symptomatic and neurological responses to hypoglycaemia in non-diabetic adults (modified from Chapter 7 Impaired Awareness of

Hypoglycaemia, p. 142, Fisher and Frier 2007 Hypoglycemia in Clinical Diabetes, John Wiley and Sons)

Diminished or absent warning symptoms of hypoglycaemia are major factors contributing to the risk of further severe episodes. A useful clinical “rule of thumb” is to describe patients whose warning symptoms develop at or below 55 mg/dl (3 mmol/l), around the threshold for onset of cognitive dysfunction, as having impaired awareness. Experimental studies involving non-diabetic individuals have demonstrated that counterregulatory and symptomatic responses to hypoglycaemia can be attenuated by antecedent hypoglycaemia on the previous day [32]. Some responses, such as sweating, may be depressed for as long as 8 days [33]. These observations have been confirmed in both individuals with Type 1 and Type 2 diabetes [34, 35]. Thus patients may enter a vicious cycle where hypoglycaemia begets more hypoglycaemia. Subsequent studies have demonstrated reduced hypoglycaemic awareness can be reversed (at least in part) by scrupulous avoidance of hypoglycaemia for 2–3 weeks although this sometimes occurred even without restoration of counterregulatory hormone release [36–38].

## Causes of Hypoglycaemia

As described above, hypoglycaemia arises where there is an excess of insulin compared to circulating blood glucose. In the clinical situation it is frequently possible to establish a contributory cause which can be assigned one of the following categories [26]:

- Excess exogenous insulin (or insulin secretagogue)—wrong dose, wrong time or formulation
- Increased insulin sensitivity—e.g. nighttime, post-exercise, weight loss, early pregnancy
- Decreased exogenous carbohydrate intake—e.g. missed meal, vomiting, fasting, malabsorption
- Decreased endogenous glucose production—e.g. alcohol which depresses hepatic gluconeogenesis
- Increased glucose utilisation—e.g. exercise

## Nocturnal Hypoglycaemia

Nocturnal hypoglycaemia is common—in the Diabetes Control and Complications Trial around half of severe episodes occurred at night [39].

In a more recent study involving adults with Type 1 diabetes aiming for tight glycaemic targets, most participants experienced nocturnal hypoglycaemia with low glucose detected on 8 % of nights by continuous glucose monitoring [40]. Patients are less likely to be alerted by early/mild hypoglycaemic symptoms while asleep and children in particular may go many hours without eating overnight. Current basal insulins are limited in their ability to provide continuous physiological basal replacement. Further, counterregulatory hormonal and symptomatic responses at night are reduced due to both to the effect of supine posture and sleep. In one study, epinephrine responses were three to four times lower at night while asleep compared with when awake [41]. Studies of overnight monitoring in children with Type 1 diabetes have reported frequent, prolonged nocturnal episodes, lasting more than three hours [42], presumably due to the combined contribution of the factors identified above.

## Alcohol

Alcohol has been implicated in up to a fifth of severe hypoglycaemic episodes requiring hospital admission [43]. Alcohol impairs both awareness of hypoglycaemia [44] and the ability of the person to self-treat due both to its inebriating effects and by suppressing gluconeogenesis. Alcohol also has a delayed effect on hypoglycaemia, often described as the “morning after the night before” phenomenon. Alcohol suppresses lipolysis which in turn suppresses hepatic glucose output [45], an effect which may extend into the following day. In one study of adults with type 1 diabetic, alcohol doubled the risk of hypoglycaemia in the following 24 h [46].

## Exercise

Exercise has clear cardiovascular benefits in both types of diabetes and is encouraged. However, it can increase the risk of hypoglycaemia due to increase in insulin sensitivity and exercise-mediated activation of glucose utilisation in skeletal muscle. In non-diabetic individuals, exercise

stimulates sympathetic activation to inhibit insulin secretion and stimulate hepatic output of glucose via glycogenolysis. In insulin-treated diabetic patients, the prevailing insulin levels are independent of and cannot be suppressed by exercise [47]. This contributes to a fall in glucose and acute hypoglycaemia during exercise but post-exercise hypoglycaemia (6–15 h later) is also a risk due to preferential repletion of muscle glycogen stores over the liver and an increase in insulin sensitivity. Exercise may also blunt subsequent counterregulatory defences to hypoglycaemic episodes [48].

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## Risk Factors for Hypoglycaemia

Much of the pathophysiology described is common to most individuals with diabetes, yet for some individuals, hypoglycaemia is extremely rare, while others experience multiple, disruptive and severe events. The likelihood of developing hypoglycaemia depends upon a number of contributory factors. These include those that determine the physiological capacity to counterregulate and generate awareness, pharmacology of glucose lowering agents, the ability of the individual to self-manage their diabetes and recognise and treat hypoglycaemia as well as psychological characteristics, which remain poorly understood.

## Long Duration of Diabetes

One of the most important contributors to hypoglycaemic risk is duration of diabetes. In an observational UK study, adults with a duration of type 1 diabetes for over 15 years were three times more likely to experience severe hypoglycaemia compared to those with diabetes for less than 5 years [9]. This presumably reflects loss of beta cell function and counterregulatory defences with type 1 diabetes. In advanced type 2 diabetes, glucagon responses to hypoglycaemia are also progressively impaired as patients become insulin deficient [49]. The risk has been shown to be highest in those using insulin for over 5 years as rates of severe hypoglycaemia approach those of individuals with newly diagnosed type 1 diabetes [9].

## Hypoglycaemia Unawareness

Nearly 20 % of patients with type 1 diabetes develop hypoglycaemia unawareness, the prevalence increasing with duration of diabetes [50]. A recent study also suggests that around 10 % of adults with type 2 diabetes also have difficulty recognising hypoglycaemia [51]. A number of scoring systems have been developed to quantify hypoglycaemia unawareness, with the Gold [52] and Clarke scores [53] being most widely adopted. Hypoglycaemia unawareness has been shown to increase the risk of severe hypoglycaemia by fivefold to sixfold in prospective surveys [52, 53]. One of the ironical consequences is that individuals with unawareness are often excluded from trials of new therapy such as insulin analogues or continuous glucose monitoring which have the potential to reduce the risk of hypoglycaemia.

## Renal Failure

Renal failure is often under-recognised as a contributor to hypoglycaemia. Renal failure reduces metabolism of insulin and clearance of metabolites of drugs such as sulphonylureas. It also affects reabsorption of filtered glucose as well as gluconeogenesis (the kidneys provide as much as 30 % of glucose production due to gluconeogenesis). In type 2 diabetes, it is estimated that the risk of severe hypoglycaemia is increased by twofold to threefold in those with eGFR <60 ml/min  $1.73 \text{ m}^2$  [54]. Management of diabetic patients with end stage renal failure on dialysis is particularly challenging. It usually necessitates major reductions in insulin doses and avoidance of sulphonylureas [55].

## Treatment Factors

Insulin and insulin secretagogues unsurprisingly are far more likely to cause hypoglycaemia. Insulin “sensitisers” such as metformin and thiazolidiones have a minimal risk of hypoglycae-

mia. In the UK Prospective Diabetes Study, rate of self-reported hypoglycaemia was 0.3 % in patients on metformin monotherapy in first 6 years of diagnosis [56]. Emerging data on the incretin based therapies dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogues indicate that risk of significant hypoglycaemia are also very low [57], unless patients are being treated concurrently with sulphonylureas or insulin.

It has been estimated that 39 % of patients on sulphonylureas alone will experience mild hypoglycaemia and severe hypoglycaemia will occur in 0.8 % each year [9]. The third generation sulphonylureas (gliclazide, glimeperide) and metaglinides have a lower risk of hypoglycaemia compared to older drugs such as glyburide (glibenclamide), presumably due to shorter duration of action. The risk is increased when sulphonylureas are part of combination therapy, particularly with insulin [58].

Insulin analogues have a pharmacokinetic profile that should lower the potential for hypoglycaemia compared to human insulins. The rapid acting insulin analogues (aspart, lispro, glulisine) separate into single molecules more readily and hence are less likely to accumulate. In a meta-analysis comparing lispro with regular human insulin, the frequency of hypoglycaemia was modestly reduced (3.1 % versus 4.4 %) [59]. The peakless long acting analogues also confer a slightly lower risk for hypoglycaemia compared with isophane insulins [60]. Most if not all the benefit is generally observed for nocturnal episodes and troublesome nocturnal hypoglycaemia is a robust indication for the use of insulin analogues. Differences also exist according to the type of insulin regimen. In the 4 T study, once daily basal insulin, when initiated in type 2 diabetic patients, was associated with the lowest risk of hypoglycaemia. The risk of hypoglycaemia was higher with twice daily biphasic regimes and highest in those on prandial-basal regimes, however, fewer reached HbA1c targets in the biphasic group [61].

## Psychosocial Factors

The risk of hypoglycaemia is clearly affected by the ability of the patient to recognise and self-treat. This applies particularly to the elderly and cognitively impaired. In trials of intensive glycaemic control in type 2 diabetes, patients with cognitive impairment were at higher risk of hypoglycaemia requiring assistance [62] and similar findings have been reported in community studies [63]. In a German study, one-third of type 2 diabetic patients who experienced severe hypoglycaemia lived in a nursing home or were for cared for by a home care service [64]. Patients with type 2 diabetes are more likely to require hospital care for hypoglycaemia compared with type 1 diabetic patients.

Probably one of the most important and least studied contributing factors are psychological factors which drive patients to maintain tight glycaemic targets despite the obvious risks even in those with major recurrent episodes [65]. There is some evidence that identifying these factors and addressing them specifically can reduce hypoglycaemic risk. However, much further work needs to be undertaken in understanding this important area and developing interventions to address it.

## Clinical Assessment

Assessment of hypoglycaemia should be a part of every diabetes review. The clinician should establish (1) the frequency and nature of hypoglycaemic episodes and (2) the overall risk of hypoglycaemia. Figure 34.2 illustrates key points to clinical assessment. Part of this should include their daily insulin administration routine. The timing of prandial doses is important. Delayed or missed meals can result in the peak of insulin action coinciding with having little food in the system. Alternatively, patients who prefer to inject postprandially may experience episodes if the insulin peaks in the post-absorptive phase. Recurrent hypoglycaemia can also occur if

patients administer boluses of short-acting insulin too close together, sometimes known as insulin “stacking”. This tends to occur where patients over-correct high glucose values by repeated insulin boluses. Injecting into areas of lipohypertrophy can lead to unpredictable absorption.

Hypoglycaemia awareness should be assessed (Fig. 34.2) and corroboration from a relative or partner is often useful [66]. Diabetes duration, treatment regime and overall glycaemic control will determine a patient's risk of hypoglycaemia. However, if there is a sudden increase in hypoglycaemia that appears out of proportion to the diabetes history, other medical causes should be sought such as renal failure, hepatic failure, malabsorption, hyperthyroidism or adrenal insufficiency. Certain drugs can also increase the potential for hypoglycaemia on their own or through interactions with glucose lowering agents (Fig. 34.2).

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## Management

### Treatment of Acute Hypoglycaemia

All episodes of hypoglycaemia should be treated promptly. Mild hypoglycaemic episodes in a conscious, co-operative patient can be easily treated by rapid-acting carbohydrate (15–20 g). Figure 34.3 lists some examples of suitable treatments that are accessible and portable. Patients are often tempted to “over-treat” hypoglycaemia with excessive carbohydrate but this can lead to rebound hyperglycaemia and worsen glucose control. Rapid-acting carbohydrate should be repeated if blood glucose remains low 10–15 min later. Once blood glucose is restored to the normal range, this should be followed up with long-acting carbohydrate if a meal is not due within 1 h. In patients who are un-cooperative but able to swallow, oral glucose gels can be used. Unconscious patients should be treated with intramuscular glucagon or intravenous glucose with repeated doses of 10 % glucose solution now replacing the injection of 50 % glucose



<p><b>Clinical information:</b>  Type 1 or 2 diabetes  Duration of diabetes  Duration of insulin treatment  Hypoglycemic potential of diabetic treatment: insulin/sulphonylureas (high) vs metformin/DPP-4 inhibitors/GLP-1 analogues/thiazolidiones (low)  Other drugs (e.g. quinine, trimethoprim, salicylates)  Psychosocial risk factors e.g. living alone, cognitive impairment</p> <p><b>Enquire:</b>  Hypoglycemia  - Frequency  - Severity: self-treated, requiring assistance of family or paramedics  - Timing: nocturnal, relation to meals, exercise, alcohol  Review glucose monitoring diary</p> <p><b>Assess hypoglycemia awareness:</b>  - At what blood sugar level do you start noticing symptoms of hypos?  - Have there been times when your blood sugar is below 3mmol without any warnings?  - Are there episodes of hypoglycemia that others have noticed before you?</p> <p><b>Impact of hypoglycemia on lifestyle:</b>  Driving, high-risk occupations  Explore fear/anxiety surrounding hypoglycemia</p> <p><b>Examine:</b>  Injection site for lipohypertrophy</p> <p><b>Laboratory tests:</b>  Renal function  Liver function  <i>Consider the following if unexplained increase in hypoglycemia</i>  Thyroid function test  9am cortisol or short synacthen test  Coeliac screen  Insulin binding antibodies</p>
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**Fig. 34.2** Clinical assessment of patients with hypoglycaemia

which was particularly likely to cause thrombophlebitis. In patients who are malnourished or alcohol-dependent, liver glycogen stores are depleted and glucagon may be ineffective. Intravenous glucose is preferable if venous access is available.

## Prevention of Hypoglycaemia

It is clearly important to avoid recurrent hypoglycaemic episodes and a previous history of hypoglycaemia strongly predicts future risk [67].

**Immediate management of acute hypoglycemia**

- *Conscious, co-operative, able to swallow*  
15-20 g rapid acting carbohydrate  
e.g. 150-200ml pure fruit juice  
90-120ml Lucozade  
5-6 glucose tablets  
3-4 heaped teaspoons of sugar
- *Conscious, uncooperative, still able to swallow*  
1.5-2 tubes oral dextrose gel
- *Unconscious, seizures*  
Glucagon 1mg IM  
or  
10% Dextrose IV (150ml) or 20% dextrose IV (75ml) over 10-15min

Repeat rapid acting glucose if blood glucose less than 70mg/dL (<4mmol/l) after 15 minutes. Seek further medical help if blood glucose remains low after 3 cycles.

**Recovery:**

- Follow up with long acting carbohydrate (e.g. 2 biscuits, 1 slice of toast) unless meal within 1 hour
- Review diabetic treatment regime

**Fig. 34.3** Acute management of diabetic hypoglycaemia

Education is the key to effective self-management. In type 2 diabetes, a review of treatment regimens and glycaemic targets can reduce hypoglycaemia in many cases. In type 1 diabetes patients with long disease duration and multiple risk factors, a combination of strategies, including trial of newer insulin delivery/glucose monitoring technologies may be required.

## Education

Many cases of hypoglycaemia are attributed to errors in insulin usage (see above) and can be addressed by educating patients about the correct time and site of insulin administration. Specific strategies may be adopted to reduce hypoglycaemia associated with alcohol and exercise. Patients should have sufficient carbohydrate prior to alcohol and insulin may need to be reduced. The effect of exercise on glu-

cose is affected by the duration and intensity of physical activity, and often a suitable regimen can only be determined with trial and error. Patients may need to consume extra carbohydrate prior to exercise to allow for a margin for glucose to fall. Rapid-acting or background insulin may need to be reduced depending on their exercise regime. Patients should also avoid exercising at the peak of insulin action and injecting in the exercising muscle.

Structured education programmes that integrate education on carbohydrate estimation and insulin dose adjustment, as well as hypoglycaemia advice, can make a difference to reducing hypoglycaemia. The Insulin Treatment and Training Programmes developed in Germany and its British adaptation, the Dose Adjustment for Normal Eating (DAFNE) programme, offering flexible insulin training for type 1 diabetic patients, have reported reduced rates of severe hypoglycaemia [68] and improved hypoglycaemia recognition in nearly half of those who were unaware [69]. Blood Glucose Awareness Training (BGAT) has been shown to reduce severe hypoglycaemic episodes through teaching patients to identify their individual symptoms (internal cues) and how to anticipate blood glucose extremes based on food, exercise, and insulin regimes (external cues) [70]. It may also owe its success at least in part the training in self-management which accompanies it. The psychological effects of hypoglycaemia are complex and to successfully prevent hypoglycaemia requires a multifaceted approach. Biopsychosocial interventions such as the HyPOS programme, which addresses dysfunctional beliefs about the causes and consequences of hypoglycaemia, have also been effective [71].

## Individualised Glycaemic Targets

There is a consistent relationship between intensive glycaemic targets and increased risk of hypoglycaemia in clinical trials [72], although the relationship is less clear in observational studies of clinical practice [67]. The risk and benefits of intensive glycaemic control in pre-

venting complications versus risk of hypoglycaemia needs to be weighed for individual patients and discussed with them. The American Diabetes Association and European Association for the Study of Diabetes have advocated an individualised approach to glycaemic targets [73]. A HbA1c of <7 % remains the recommended goal for the majority of patients. However, in patients with a history of severe hypoglycaemia, limited life expectancy, extensive comorbidities, glucose targets which result in HbA1c concentrations of 7.5–8 % may be safer and more appropriate [73, 74].

### **Glucose Lowering Agents with Lower Hypoglycaemic Potential**

The choice of treatment regimen should also involve a risk benefit assessment. In patients with type 2 diabetes, hypoglycaemic risk can be lowered through the use of insulin sensitisers and incretin based therapies as opposed to insulin secretagogues. Clinicians should be cautious when introducing add-on therapy as the risk is cumulative. Dose reductions may be necessary and some agents, particularly sulphonylureas may need to be stopped. Switching to analogue insulins can also reduce the risk of hypoglycaemia particularly at night. The long acting analogues (glargine, detemir) have been associated with a risk reduction of 30 % in trials in type 1 and type 2 diabetic patients [75, 76]. Analogue insulins may not be cost-effective in all patients, but are indicated in those at high risk of hypoglycaemia.

### **Continuous Subcutaneous Insulin Therapy**

Continuous subcutaneous insulin therapy (CSII) has the advantage over multiple daily injections in its ability to vary basal insulin delivery rates over short intervals. This may be particularly useful in the management of noc-

turnal hypoglycaemia. Basal rates can be reduced in the early hours of the morning when risk is the highest. Some early studies reported surprisingly little effect on hypoglycaemia, perhaps because of a failure to train patients in the essential related skills of carbohydrate and insulin dose adjustment. In a recent meta-analysis of CSII versus standard multiple daily injections in individuals with hypoglycaemic problems, CSII reduced severe hypoglycaemia by threefold to fourfold [77].

### **Real-Time Continuous Glucose Monitoring**

Real time continuous glucose monitoring (RT-CGM) has recently emerged as an alternative technology to conventional self-monitoring of blood glucose (SMBG). RT-CGM can measure interstitial glucose every few minutes via a subcutaneous sensor which displays the prevalent glucose via a portable device. The RT-CGM can activate alarms when the glucose falls too low or is too high. Furthermore, these devices contain predictive algorithms which can warn patients of impending hypoglycaemia or hyperglycaemia. Thus far, RT-CGM has shown, rather surprisingly, limited effectiveness in clinical trials. In a meta-analysis of randomised controlled trials comparing RT-CGM with SMBG in type 1 diabetes, there was no significant difference in rates of severe hypoglycaemia [78]. However, the absolute hypoglycaemia event rates in these trials were low and often excluded the most vulnerable groups (e.g. patients with a history of severe hypoglycaemia). There are also inherent limitations in CGM technology. There is a lag between interstitial and blood glucose which is exaggerated during rapid glucose fluctuations. CGM also has lower accuracy in the extreme hypoglycaemic range. It appears that the effectiveness of RT-CGM relies heavily on patient adherence [78] and so may prove a useful tool in selected, motivated patients.

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## New and Future Therapies

### Sensor Augmented Pumps and Closed Loop Devices

Recently, attempts have been made to combine insulin pump devices with RT-CGM monitoring systems. A version that has already been trialed is the sensor-augmented pump (SAP) which transmits interstitial glucose values to the user but does not automatically adjust insulin delivery rates. In the STAR-3 study where SAP were compared with multiple daily injections and conventional blood glucose monitoring, overall HbA1c was improved with SAP but rates of severe hypoglycaemia were not significantly different [79]. The latest pumps have introduced a “low glucose suspend” technology, such that basal insulin is automatically suspended when interstitial glucose, as detected by RT-CGM, falls below a defined threshold. Several trials have shown encouraging results albeit over the short-term, reducing the duration and severity of hypoglycaemia at night [80] and throughout the day [81].

The holy grail of insulin delivery systems, or the “artificial pancreas”, is one which can automatically adjust rates of insulin delivery based on glucose values. These “closed-loop” systems have been tested in overnight settings. Early trials are promising. In the first randomised controlled trial of closed loop versus CSII in children and adolescents, time spent in hypoglycaemia was halved [82]. Although closed loop systems have been tested in a variety of simulated situations (such as post exercise or an evening meal with alcohol) [83], larger trials are awaited of fully automated systems conducted in home settings.

Hypoglycaemia in type 1 diabetes is not only the consequence of iatrogenic hyperinsulinaemia but is also a consequence of defective glucagon counterregulation. Bihormonal pumps are currently in development which can not only switch off insulin but also release glucagon in the event of low glucose. A bihormonal closed loop system has been tested in six patients with type 1 diabe-

tes without any endogenous insulin secretion, which showed minimal hypoglycaemia throughout the 2 day use, even following exercise [84]. Clearly, new insulin delivery/glucose sensing technologies offer promising solutions to preventing hypoglycaemia, although most still require patient input and collaboration, and will not be the answer for all.

### Islet Cell and Pancreatic Transplant

Islet cell transplantation is a treatment option in type 1 diabetic patients who suffer disabling hypoglycaemia despite best medical therapy. Pancreatic transplantation has been practiced since the 1960s. However, successful islet transplantation has only recently been possible following refined cell isolation and immunosuppression protocols pioneered by the Edmonton group [85]. Islet cell transplantation restores the major physiological defence of automatic inhibition of endogenous insulin and may also restore glucagon secretion during hypoglycaemia, at least in part [86]. Although one of the benefits of islet cell transplantation is insulin independence, the benefits of protection from severe hypoglycaemia even apply to those who remain insulin dependent. Based on data from the UK programme, it is estimated that 90 %, 75 % and 50 % of transplanted patients will be free from severe hypoglycaemia at 1, 3 and 5 years respectively [87]. Pancreatic transplantation can offer similar protection from hypoglycaemia and higher rates of insulin independence, but the operation carries greater morbidity and mortality.

### Lifestyle Implications

The risk of hypoglycaemia in individuals with diabetes has led to major restrictions on different aspects of their lives, including employment, recreational and daily activities. One key restriction concerns driving. Studies employing driving

simulators have reported impaired performance on certain components such as braking and speeding at glucose levels as high as 70mg/dl (4 mmol/l) in those with type 1 diabetes. Participants were also slow to recognise and correct a low glucose [88]. Current guidance recommends that patients should always check their blood glucose to be a minimum of 90 mg/dl (5 mmol/l) or above before driving [88]. Rapid acting and more substantial carbohydrate should always be available in the vehicle. For longer journeys, glucose should be checked two hourly. If patients experience hypoglycaemia while driving, in the UK they are required to remove themselves from the driver's seat and not drive for 45 min after glucose levels are restored to allow for full recovery of cognitive function. In patients who have experienced recurrent severe hypoglycaemia or absent hypoglycaemia awareness, patients are required to inform vehicle licencing authorities, who will generally withdraw their driving licence. It is the responsibility of the clinician to make an assessment of fitness to drive and advise patients to inform the vehicle licencing authorities as appropriate.

## Conclusion

Hypoglycaemia is a common and major side effect of insulin and sulphonylurea treatment that remains a formidable barrier to optimal glucose control, even in the modern era of intensive glycaemic therapy. Physical and psychological consequences of hypoglycaemia are substantial for patients and their families, which extend beyond the acute episode. The burden of hypoglycaemia in elderly patients with type 2 diabetes is also considerable.

A recent focus in developing agents with lower hypoglycaemic potential may benefit individuals with Type 2 diabetes. For people with Type 1 diabetes, technological advances may enable better detection of hypoglycaemia and more physiological replacement of insulin and/or other counter-regulatory hormones. There will be a time when hypoglycaemia will no longer figure so prominently in the lives of individuals with diabetes although for most, that day is still many years off.

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## Introduction

The diabetic neuropathies are heterogeneous disorders which present with variable clinical manifestations affecting different parts of nervous system [1]. (Table 35.1). Involvement of the peripheral and autonomic nervous systems is probably the most common complication of diabetes. The duration and severity of hyperglycemia are major risk factors for the development of diabetic neuropathy in patients with type 1 or type 2 diabetes [2]. The United Kingdom Prospective Diabetes Study showed that other factors, including dyslipidemia and hypertension as part of the metabolic syndrome, are instrumental in the onset and progression of diabetic neuropathy in patients with type 2 diabetes [3].

The pathogenesis of the diabetic neuropathy is complex. The implicated metabolic factors include the following: accumulation of advanced glycosylation end products, accumulation of sorbitol,

disruption of the hexosamine pathway, disruption of the protein kinase C pathway, activation of the poly (ADP-ribose) polymerase pathway, increased oxidative stress. This occurs in a fiber-selective pattern that preferentially affects distal sensory and autonomic fibers, leading to the progressive loss of sensation that underlies the clinical manifestations of diabetic polyneuropathy [4].

Clinical diabetic neuropathy is categorized into distinct syndromes according to the neurologic distribution. There are many forms of diabetic neuropathy including symmetric polyneuropathy, autonomic neuropathy, radiculopathies, and focal and multifocal neuropathies. Clinical and subclinical neuropathy has been estimated to occur in 10–100 % of diabetic patients, depending upon the diagnostic criteria and patient populations examined. Prevalence is a function of disease duration, about 50 % of patients with diabetes will develop neuropathy, and about 25 % of those patients will experience no pain at all [5]. Most common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy [1]. The chronic sensorimotor distal polyneuropathy represents a diffuse symmetric and length-dependent injury to peripheral nerves that has major implications on quality of life, morbidity, and costs from a public health perspective [1, 6]. Diabetic neuropathy can affect any part of the nervous system. Painful diabetic neuropathy (PDN) affects 16 % of patients with diabetes, and it is frequently unreported (12.5 %) and more frequently untreated (39 %) [7].

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**Table 35.1** Classification of diabetic neuropathy

<i>Sensorimotor neuropathy</i>
Distal symmetric polyneuropathy
Focal neuropathy
Diabetic mononeuropathy (cranial, truncal, peripheral nerves)
Mononeuropathy multiplex
Diabetic amyotrophy
<i>Autonomic neuropathy</i>
Hypoglycemic unawareness
Abnormal pupillary function
Cardiovascular autonomic neuropathy
Vasomotor neuropathy
Sudomotor neuropathy (sweat glands)
Gastrointestinal autonomic neuropathy
Gastric atony
Diabetic diarrhea or constipation
Fecal incontinence
Genitourinary autonomic neuropathy
Bladder dysfunction
Sexual dysfunction

Diabetic neuropathy should be suspect in all patients with type 2 diabetes and in patients who have had type 1 diabetes for more than 5 years [2]. In some instances, patients with diabetic neuropathy have few complaints, but their physical examination reveals mild to moderately severe sensory loss [1, 2]. Ten to 18 % of patients have evidence of nerve damage at the time their diabetes is diagnosed, suggesting that even early impairment of glucose handling, classified as prediabetes, may be associated with neuropathy.

The early recognition and appropriate management of neuropathy in the patient with diabetes is important for several reasons, nondiabetic neuropathies may be present in diabetic patients, a number of treatment options exist for symptomatic diabetic neuropathy, autonomic neuropathy may involve every system in the body, autonomic neuropathy cause substantial morbidity and increased mortality, particularly if cardiovascular autonomic neuropathy is present. Because >80 % of amputations follow a foot ulcer or injury, early recognition of at-risk patients, providing education and appropriate care may reduce ulceration and amputation [1, 8].

## Peripheral Neuropathy

This is the most common presentation of neuropathy in the diabetic patient. Up to 50 % of patients may experience symptoms. Patients may not volunteer symptoms but on inquiry admit that feet feel numb or dead. Patients with prediabetes may present with intense painful feet. The diabetic polyneuropathy is frequently insidious in onset and can lead to formation of foot ulcers and muscle and joint disease.

## When to Suspect

Diabetic neuropathy should be suspected in any patient with type 1 diabetes for more than 5 years in duration and in all patients with type 2 diabetes. Patients with prediabetes presenting with “idiopathic” painful neuropathy, diabetic neuropathy should be suspect [1, 2, 8].

The diabetic patients should be screened annually (Table 35.2) by examining pinprick, temperature and vibration perception (using a 128 Hz-tuning fork), 10 g monofilament pressure sensation at the distal halluces and ankle reflexes. Combinations of more than one test have 87 % sensitivity in detecting polyneuropathy. Loss of 10 g monofilament perception and reduced vibration perception predict foot ulcers [1, 8]. The feet should be examined for ulcers, calluses and deformities and footwear should be inspected.

The diagnosis of diabetic polyneuropathy is based on interpretation of a constellation of symptoms and signs such as loss of vibratory or light touch sensation and reduced or absent ankle tendon reflexes [1, 5]. The symptoms most frequently found are burning pain, electrical or stabbing sensations, paresthesiae or dysesthesias in the lower extremities. Accurate assessment of symptoms in diabetic neuropathy is known to be difficult. Symptoms do not always indicate underlying neuropathy, as absence of symptoms should never be assumed to indicate an absence of signs. Therefore we should rely on clinical signs to diagnose diabetic neuropathy. Confirmation can be made with and quantitative electrophysiology [5] (Table 35.3).

**Table 35.2** Symptoms of diabetic neuropathy

<i>Sensorimotor neuropathy</i>
Muscular symptoms: muscle weakness (not fatigue), atrophy, balance problems, ataxic gait
Sensory symptoms: pain, paresthesia, numbness, paralysis, cramping, night time falls, antalgic gait
<i>Autonomic neuropathy</i>
Cardiovascular symptoms: exercise intolerance, fatigue, sustained heart rate, syncope, dizziness, lightheadedness, balance problems
Gastrointestinal symptoms: dysphagia, bloating, nausea and vomiting, diarrhea, constipation, loss of bowel control
Genitourinary symptoms: loss of bladder control, urinary tract infection, urinary frequency or dribbling, erectile dysfunction, loss of libido, dyspareunia, vaginal dryness, anorgasmia
Sudomotor (sweat glands) symptoms: pruritus, dry skin, limb hair loss, calluses, reddened areas
Endocrine symptoms: hypoglycemic unawareness
Other symptoms: difficulty driving at night, depression, anxiety, sleep disorders, cognitive changes

**Table 35.3** Evaluation for diabetic neuropathy

<i>History</i>
Screen for symptoms of diabetic neuropathy (see also Table 35.4)
Review diabetes history, disease management, daily glycemic records, and previous hemoglobin A1C levels
Identify any family history of diabetes or neuropathy
Review medication history (including use of over-the-counter products and herbal or homeopathic products) and environmental exposures
Review for other causes of neuropathy, including vitamin B12 deficiency, alcoholism, toxic exposures, medications, cancers, and autoimmune disease
<i>Physical examination</i>
Vital signs and pain index
Supine and standing blood pressure for postural hypotension
Cardiovascular examination to look for arrhythmias, absent or diminished pulses, edema, or delayed capillary refilling
Cutaneous examination to look for extremity hair loss, skin or nail changes (including callus), and pretrophic (red) areas, especially between toes
Neurologic examination using the 5.07 Semmes-Weinstein (10-g) nylon filament test (10-g monofilament test)
Inspection of feet for asymmetry, loss of arch height, or hammer toes
Evaluation of all positive screening findings

**Table 35.4** United Kingdom screening score

<i>Symptoms</i>
What is the sensation felt? Maximum is 2 points
<ul style="list-style-type: none"> <li>Burning, numbness, or tingling in the feet (2 points);</li> <li>Fatigue, cramping, or aching (1 point)</li> </ul>
What is the location of symptoms? Maximum is 2 points
<ul style="list-style-type: none"> <li>Feet (2 points)</li> <li>Calves (1 points)</li> <li>Elsewhere (0 points)</li> </ul>
Have the symptoms ever awakened you at night?
<ul style="list-style-type: none"> <li>Yes (1 point)</li> </ul>
What is the timing of symptoms? Maximum 2 points
<ul style="list-style-type: none"> <li>Worse at night (2 points)</li> <li>Present day and night (1 point)</li> <li>Present only during the day (0 points)</li> </ul>
How are symptoms relieved? Maximum is 2 points
<ul style="list-style-type: none"> <li>Walking around (2 points)</li> <li>Standing (1 point)</li> <li>Sitting or lying or no relief (0 points)</li> </ul>
0–2 points: normal; 3–4 points: mild neuropathy; 5–6 points: moderate neuropathy; 7–9 points severe neuropathy

## Main Characteristics of Diabetic Polyneuropathy

The diabetic polyneuropathy can be defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes [9]. The neuropathy pain is typically worse at night and symptoms are most commonly experience in feet more than calves and lower limbs, although in some cases the hands may be affected. The physical examination may be helpful, usually reveals sensory loss of vibration, pain, temperature perception, and loss of deep tendon reflexes [9].

## Screening Tests

The need to identify simplified criteria has resulted in the development of at least two simple screening test scores, one is the United Kingdom screening score (Table 35.4) [10] and the other is the Michigan screening score (Table 35.5) [11].

**Table 35.5** Michigan Neuropathy screening score

Do the feet show dry skin, callus, fissure, infection, or deformities?
The presence of any of these indicators of neuropathy is scored as one point and an additional point is added if an ulcer is present
What is the vibration sense on the dorsum of the great toes?
Reduced (0, 5 points); absent (1 point)
What is the Achilles tendon reflex?
Absent (1 point); present with reinforcement (0, 5 points)
>2 points—neuropathy

In the United Kingdom score the peripheral neuropathy is considered to be present if there are moderate or severe signs ( $\geq 6$  points), even in the absence of symptoms, or if there are at least mild signs ( $\geq 3$  points) in the presence of moderate symptoms ( $\geq 5$  points). A neurologic sign score of 8 or more indicates that the patient's feet are at high risk for ulceration.

## Differential Diagnosis

Other causes of neuropathy in a diabetic patient should be considered if there is any aspect of history or clinical presentation suggesting features atypical of diabetic neuropathy.

The chronic inflammatory demyelinating polyneuropathy and neuropathy due to vitamin B12 deficiency, hypothyroidism and uremia occur more frequently in patients with diabetes than in the general population [1, 5].

## Acute Sensory Neuropathy and How to Distinguish from Chronic Sensorimotor Diabetic Polyneuropathy

Acute sensory neuropathy may occur after periods of poor metabolic control (e.g., Ketoacidosis) or sudden change in glycemic control, also called insulin neuritis [12]. It presents few signs on physical examination. It is a rare condition and is characterized by the acute onset of severe sensory symptoms with marked nocturnal exacerbation [12]. There are others types of acute diabetic

neuropathy, diabetic neuropathic cachexia and diabetic anorexia, when occurs severe weight loss unintended and intentional respectively [1].

## Treatment

There three main elements in the treatment of diabetic polyneuropathy: glycemic control, foot care and treatment of pain.

## The Role of Glycemic Control

The Diabetic Control and Complications Trial (DCCT) has shown that in Type 1 diabetic patients the risk of diabetic polyneuropathy and autonomic neuropathy can be reduced with improved blood glucose control [1, 2]. The occurrence of diabetic neuropathy was reduced by 60 % over a 10 year period with rigorous blood glucose control. Similar findings were noted in the Stockholm Diabetes Intervention Study [13]. The importance of glycemic control in type 2 diabetic patients is less strong.

The importance of intensive control glycemic in established neuropathy is unclear. Uncontrolled studies suggest that neuropathy symptoms may improve with intensive antidiabetic therapy [14, 15]. Although controlled Trial evidence is lacking, several observational studies suggest that neuropathic symptoms improve not only with optimization of control, but also with the avoidance of extreme blood glucose fluctuations [1].

## Foot Care

Once a patient has diabetic neuropathy, foot care is even more important to prevent ulceration, infection, and amputation. The lifetime risk of a foot ulcer for diabetic patients may be as 25 % [5]. The diabetic patients need to inspect their feet for the presence of dry or cracking skin, fissures, plantar callus formation, and signs of early infection between the toes and around the toe nails. Foot amputations are an important cause of morbidity in patients with diabetes mellitus [8].

Several risk factors are predictive of ulcers and amputation. Foot amputations are preventable with early recognition and therapy of risk factors. The most important are previous foot ulceration, sensitive neuropathy, (it promotes ulcer formation by decreasing pain sensation and perception of pressure), foot deformity and vascular disease [5, 16]. Others factors have been considered as duration of diabetes, glycemic control, presence of claudication, and history of cigarette smoking. Systematic screening examinations for neuropathic and vascular involvement of the lower extremities and careful inspection of feet may substantially reduce morbidity from foot problems [17, 18].

### Painful Diabetic Neuropathy

Only a small fraction of patients with diabetic polyneuropathy have painful symptoms. There are many treatment options available however, before initiating therapy, it is important to confirm that the pain is due to diabetic polyneuropathy. A disc lesion should be considered if the pain has development in relation to recent trauma or its onset is abrupt. Peripheral vascular disease should be considered.

A rational approach to treating the patient with painful diabetic neuropathy requires a systematic, stepwise approach. There are pharmacological and nonpharmacological therapies to reduce pain and improve physical function [17].

The pharmacological agents include anticonvulsants, antidepressants, opioids, antiarrhythmics, cannabinoids, aldose reductase inhibitors, protein kinase C beta inhibitors, antioxidants (alpha-lipoic acid), transketolase activators (thiamines and allithiamines), topical medications (analgesic patches, anesthetic patches, capsaicin cream, clonidine) [1] (Table 35.6).

The nonpharmacologic modalities are infrared therapy, shoe magnets, exercise, acupuncture, external stimulation (transcutaneous electrical nerve stimulation), spinal cord stimulation, biofeedback and behavioral therapy, surgical decompression, and intrathecal baclofen [6].

**Table 35.6** Drug therapy for painful diabetic neuropathy

<i>Anticonvulsants</i>	
Pregabalin	–300–600 mg/day
Gabapentin	–900–3,600 mg/day
Valproate	–500–1,200 mg/day
<i>Antidepressants</i>	
Amitriptylin	–25–100 mg/day
Vanlafaxine	–75–225 mg/day
Duloxetine	–60–120 mg/day
<i>Opioids</i>	
Tramadol	–210 mg/day
Oxycodone	–37–120 mg/day
Morphine sulfate	–titrated to 120 mg/day
Dextromethorphan	–400 mg/day
<i>Others</i>	
Capsaicin	–0.075 % QID
Isosorbide dinitrate spray	
Electrical stimulation percutaneous nerve stimulation	× 3–4 weeks

### Antidepressants

Based on randomized controlled trials, the antidepressants amitriptyline, venlafaxine, and duloxetine are beneficial for reducing pain associated with diabetic neuropathy [6]. Data are insufficient to recommend one of these agents over the others. A systematic review found that tricyclic antidepressants were more effective for short-term pain relief than traditional or newer generation anticonvulsants [18]. The therapeutic effect usually occurs sooner (within 6 weeks) and at lower doses than is typical when these drugs are given for the treatment of depression.

Duloxetine is probably effective in lessening the pain of diabetic neuropathy [6]. Duloxetine showed rapid onset of action and sustained benefit, and it was also effective in relieving pain at night. Amitriptyline appears to be effective as duloxetine for treatment of painful diabetic neuropathy, and is less expensive [6].

The efficacy of venlafaxine was evaluated for two studies. In a randomized controlled Trial, Venlafaxine at higher doses was associated with significant benefit in pain relief compared with placebo [19]. In a study, venlafaxine plus gabapentine showed 18 % more relief than with placebo plus gabapentina [20].

There insufficient evidence to support or refute the use of imipramine, nortriptyline, or fluoxetine.

Tricyclic agents such as amitriptyline and desipramine (mainly amitriptyline) are recommended in patients with severe pain. Side effects of tricyclic antidepressants include dry mouth, somnolence, and urinary retention. This class of drugs can be added to anticonvulsants, but not duloxetine. Amitriptyline is contraindicated in patients with cardiac disease, should be given duloxetine or venlafaxine.

### Anticonvulsants

Pregabalin and valproate may be useful for treating painful diabetic neuropathy. The effectiveness of pregabalin for treatment of painful diabetic neuropathy was evaluated in seven randomized clinical trials. All studies found that pregabalin relieved pain, but the effect size was small relative to placebo. There was a clear dose-related increase in effectiveness, and an increase in the incidence of most adverse events. The most common adverse events were dizziness, somnolence, and peripheral edema. Can cause sedation and confusion. Two small studies evaluated the efficacy of valproate. Both studies were conducted at the same center [21].

The role of gabapentin for the treatment of painful diabetic neuropathy is controversial [6, 22]. A small randomized trial found that gabapentin was not superior to placebo. The major side effects of gabapentin are somnolence, dizziness and ataxia [23].

There is insufficient evidence to support or refute the use of topiramate and carbamazepin for the treatment of painful diabetic neuropathy [6].

### Other Agents

Alpha-lipoic acid, a potent antioxidant has been associated with some benefit for symptomatic diabetic neuropathy. Its use may be recommended in patients with who are refractory to or intolerant of antidepressants or anticonvulsants [6, 24].

Capsaicin cream causes analgesia through local depletion of substance P, it is a component of hot peppers. Studies of capsaicin showed modest but statistically significant improvement in pain compared with placebo [6, 25]. Capsaicin can be added for patients with pain who are refractory to or intolerant of antidepressant or anticonvulsants. Side effects are burning pain, which is exacerbated by contact with warm water and hot weather.

One trial showed that lidocaine patches significantly improved pain and quality of life in 56 patients with painful diabetic neuropathy [26].

Opioids have been studied for the treatment of painful diabetic neuropathy. Tramadol and oxycodone were more effective than placebo for relieving pain. However the trials supporting the efficacy of opioids such as tramadol and oxycodone are all limited by short-term follow-up [27].

Several others agents have been tested in patients with painful diabetic neuropathy. Acetyl-L-carnitine, the acetylated ester of the amino acid L-carnitine was associated with significant improvement in pain scores [28]. Isosorbide dinitrate topical spray showed a moderate effect in lessening the pain relative to placebo [6]. Nonsteroidal antiinflammatory drugs (NSADs) ibuprofen and sulindac can lead to substantial pain relief in patients with diabetic neuropathy, however they should be used with caution because concerns that they may impair nerve circulation and worsen nerve injury due to inhibition of prostacyclin synthesis [6] and also because the risk of renal damage.

### Nonpharmacological Therapy

Percutaneous electrical nerve stimulation may be effective for pain relieve in diabetic neuropathy [29]. However, the percutaneous techniques evaluated in trials are not widely available in clinical practice.

One study using pulsed electromagnetic fields compared with a sham device failed to demonstrate an effect in patients with painful diabetic neuropathy. Likewise, Reiki therapy and laser treatment did not show any effect as well [6].

Finally, sorbitol accumulation may play a role in diabetic neuropathy, but the use of aldose reductase inhibitors to prevent sorbitol formation have so far failed to show clinical benefits.

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## Autonomic Neuropathy

### Cardiovascular Autonomic Neuropathy

Diabetic autonomic neuropathy associated with significant morbidity and mortality in some patients with diabetes. It is classified as subclinical or clinical depending upon the presence or absence of symptoms [1].

The symptoms of autonomic dysfunction should be elicited accurately during consultation of a diabetic patient. There is a large number of symptoms affecting many different organ systems, including: cardiovascular, gastrointestinal, genitourinary, pupillary, sudomotor and neuroendocrine systems. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, and hypoglycemic autonomic failure [1].

Cardiovascular autonomic neuropathy is defined as the impairment of autonomic control of the cardiovascular system. It is the most studied and clinically important form of diabetic autonomic neuropathy. The prevalence of cardiovascular autonomic neuropathy varies widely depending on the cohort studied and the tests used, diagnostic criteria, and the population studied [30].

The cardiovascular autonomic neuropathy may be subclinical, in this case the disease is defined by cardiovascular reflex testing, which may have prognostic implications. Clinically is associated with resting tachycardia (>100 bpm). Persistent sinus tachycardia can occur and there may be no variation in heart rate during activities that normally increase parasympathetic vagal tone, such as deep breathing and Valsalva maneuver. Others manifestations are: exercise intolerance, orthostatic hypotension, intraoperative cardiovascular instability [1].

Cardiac denervation can occur in diabetic patients with autonomic neuropathy. It is associated with silent myocardial infarction and ischemia, and increased mortality [31]. Hypotension and hypertension after vigorous exercise are more likely to develop in patients with autonomic neuropathy, particularly when starting an exercise program. Cardiac autonomic function testing should be performed when planning an exercise program for individuals with diabetes about embark on a moderate to high intensity exercise program [1].

The presence of cardiovascular autonomic neuropathy may be associated with adverse renal and cerebrovascular outcomes [32].

A patient's history and physical examination are ineffective for early detection subclinical autonomic neuropathy. It may only be detected by using cardiovascular reflex tests or tests of peripheral sympathetic function [30]. There are many tests that assess parasympathetic integrity, including: cardiovascular tests of heart rate response, orthostatic hypotension test, QT interval, ambulatory blood pressure monitoring for dipping status, heart rate variability time and frequency domain indices. These tests are relatively insensitive to sympathetic deficits. The choice of tests remains debatable and dependent upon the indication. Of these tests, heart rate variability in response to deep breathing has the greatest specificity (approximately 80 %). Regular tests for heart rate variability provide early detection and thereby promote timely diagnostic and therapeutic interventions. These tests may also facilitate differential diagnosis and attribution of symptoms (e.g., erectile dysfunction, dyspepsia, and dizziness) to autonomic dysfunction [33].

Direct assessment cardiac sympathetic integrity has become possible with the introduction of radiolabeled analogues of norepinephrine, which are actively taken up by the sympathetic nerve terminals of the heart. These tests have limited clinical utility because they are expensive and not widely available.

At time of diagnosis of type 2 diabetes and within 5 years after diagnosis of type 1 diabetes, patients should be screened for cardiovascular autonomic neuropathy [1].

Exercise program can improve both early and more advanced cardiovascular autonomic neuropathy. There are general recommendations: making changes in posture slowly, tensing the legs by crossing them while actively standing on both legs. It can minimize postural symptoms. It is important discontinuation of aggravating drugs (e.g., tranquilizers, antidepressants, and diuretics) [34, 35].

Fludrocortisone (0.1–0.4 mg/day) and salt diet may be helpful in severe cases but can cause hypertension or peripheral edema. The somatostatin analogue, octreotide (50 mcg three times daily) may be helpful in diabetic patients with refractory and symptomatic postural. It may exacerbate bowel dysfunction and cause fluctuations in glycemic control [36].

### **Gastrointestinal Autonomic Neuropathy**

Any section of the gastrointestinal tract may be affected. The symptoms of gastrointestinal autonomic neuropathy vary with the site of involvement. Gastroparesis should be suspect in patients with erratic glucose control. Evaluation of gastric emptying should be done if the patients have anorexia, nausea, vomiting, early satiety, and postprandial fullness. Barium studies or referral for endoscopy may be required [1]. The patients with esophageal motility disorders have dysphagia and retrosternal pain. Others symptoms are constipation, diarrhea, or even incontinence.

The treatment of gastroparesis varies with the type of symptoms. Must be guided frequent small meals, prokinetic agents (metoclopramide, domperidone, erythromycin) [1].

Autonomic diarrhea is often nocturnal and alternating with constipation and incontinence. The treatment varies with the causative factors responsible for the diarrhea. Antibiotics for bacterial overgrowth, loperamide for aberrant motility, and biofeedback for anorectal dysfunction. When the diarrhea is intractable, octreotide is an alternative [36].

### **Genitourinary Autonomic Neuropathy**

The genitourinary tract disturbances are associated with bladder and/or sexual dysfunction. Diabetic bladder dysfunction initially presents as a decrease in the ability to sense a full bladder, and it results in incomplete emptying. These abnormalities can result in recurrent urinary tract infections and overflow incontinence. In men, the genitourinary autonomic neuropathy may cause loss of penile erection and/or retrograde ejaculation. In women, can have decrease libido and reduced vaginal lubrication [37].

Treatment consists of a strict voluntary urination Schedule coupled with bethanecol (10–30 mg three times daily). More advanced cases require intermittent catheterization or resection of internal sphincter at the bladder neck. Sexual dysfunction must be treated with sex therapy, psychological counseling and treatment with type 5 phosphodiesterase inhibition.

### **The Effect on Diabetes Control**

Episodes of hypoglycemia may be more common in patients with autonomic neuropathy. Several factors may account for this, such as diabetic gastroparesis and alterations in neuroendocrine responses, include a reduction in glucagon and epinephrine secretion in response to hypoglycemia.

### **Focal and Multifocal Neuropathies**

- The most common peripheral mononeuropathy in diabetic patients is median mononeuropathy.
- Cranial neuropathies are extremely rare.
- Electrophysiological is suggestive of demyelination and axonal degeneration.

The diabetic mononeuropathy affects the median nerve (the most common), ulnar, radial and peroneal. The cranial mononeuropathies are rare and occur in those nerves which supply the extraocular muscle (cranial nerve III, VI



and IV) [1]. Others are diabetic amyotrophy and thoracic polyradiculopathy [5, 38].

The diagnosis of diabetic mononeuropathy can be done through clinical careful evaluation and electrophysiological studies. The electrophysiological studies show a reduction in nerve conduction and amplitude suggestive of underlying demyelination and axonal degeneration. Many of these patients complain acute, asymmetric, focal pain followed by weakness involving the proximal leg and after careful clinical and electrodiagnostic examinations, are found to have a high lumbar radiculopathy (diabetic amyotrophy) [1]. Other cause of pain in diabetics is thoracic polyradiculopathy; the patients present with severe abdominal pain, and the differential diagnostic is done with gastrointestinal causes.

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#### *General recommendations*

Tight glycemic control can prevent, delay, or slow the progression of diabetic neuropathy in patients with type 1 diabetes

Patients with diabetes should be educated about proper foot care and should check their feet daily

All patients with diabetes should have an annual foot examination by a health care professional

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Elba Bandeira and Deborah Queiroz

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## Introduction

Diabetic nephropathy (DN) occurs in 20–40% of patients with diabetes and is a major cause of morbidity and mortality. It occurs not only in persons with type 1 and type 2 diabetes mellitus (DM) but also in secondary forms of DM, such as after pancreatitis or pancreatectomy [1].

The number of people known to have end-stage renal disease (ESRD) worldwide is growing rapidly, as a result of improved diagnostic capabilities, the global epidemic of type 2 diabetes (T2DM) and other causes of chronic kidney disease (CKD) [2]. Diabetes is the most frequent cause of severe CKD [1] and in Western countries is the leading cause of ESRD [3].

In the United States (US), the adjusted rate of new ESRD cases, considering diabetes as the primary diagnosis, increased by 0.5% in 2009, to 154.1 per million inhabitants. The prevalence of

the disease rises with CKD severity. In patients with an estimated glomerular filtration rate (eGFR) less than 30, 30–<45, and 45–<60, the percentage of diabetes was 40, 27, and 18, respectively, and the expenditure on Medicare for patients with CKD and diabetes in that year was US\$18 billion [4].

The progression to ESRD is similar in type 1 and type 2 diabetes. However, as T2DM is more prevalent, the majority of patients with ESRD are type 2 diabetics. The World Health Organization (WHO) has estimated that the number of diabetic patients was 135 million in 1995 and should be over 300 million in 2025 [5]. The prevalence of diabetic nephropathy has increased [1] because of the epidemic of diabetes, longer periods of disease without a good glycemic control, and improvements in the treatment of hypertension and coronary heart disease, which have prolonged the lifespan of patients with T2DM, and increased the risk of developing complications such as nephropathy and ESRD.

In many countries, such as the United States, about 50 % of patients in renal replacement therapy programs have diabetes as the major cause of their renal failure [4]. However, a greater number of patients with diabetes are in developing countries [6], which do not have sufficient resources or a health infrastructure that would enable them to provide universal renal replacement therapy. Furthermore, even in developed countries, fewer than 1 in 20 patients with DM and CKD survive to ESRD, succumbing to cardiovascular disease (CVD), heart failure, or infection, and the severity

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of diabetic renal disease significantly contributes to this outcome [1].

Hence it is of great importance to obtain an early diagnosis, appropriate management and the development of new strategies of treatment, particularly those related to the control of glycemia, blood pressure, and other comorbidities associated with diabetes, that may lead to better outcomes.

## Diagnosis

The term diabetic nephropathy is used to describe a specific renal condition caused by diabetes, characterized by hyperfiltration, persistent albuminuria of more than 300 mg/day, with a continuous decline in the glomerular filtration rate (GFR), raised arterial blood pressure (BP), and enhanced cardiovascular morbidity and mortality [7] (Table 36.1).

Persistent albuminuria in the range of 30–299 mg/24 h (microalbuminuria) is considered the earliest stage of DN in type 1 diabetes (T1DM) and a marker for development of nephropathy in T2DM and for increased CVD risk [8].

The pathophysiological mechanisms in the development of DN are multifactorial. Hyperglycemia is related to structural and functional changes such as glomerular hyperfiltration, glomerular and tubular epithelial hypertrophy, and microalbuminuria, followed by the development of glomerular basement membrane (GBM) thickening, accumulation of mesangial matrix, evident proteinuria, and eventually glomerulosclerosis and ESRD. Nevertheless, intensive therapy to improve glycemic control is able to attenuate the development of nephropathy, as assessed by urinary albumin excretion (UAE), but not fully prevent it [9] (Fig. 36.1).

**Table 36.1** Laboratory tests for screening and diagnosis of diabetic nephropathy

Albuminuria—albumin/creatinine ratio

Serum creatinine

<sup>a</sup>eGFR-MDRD or CKD-EPI

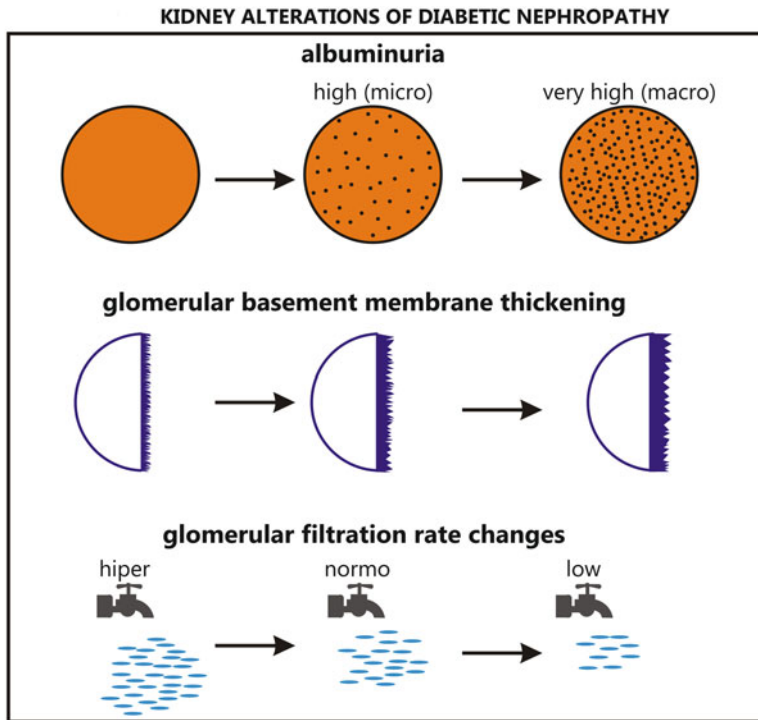
<sup>a</sup>eGFR estimated glomerular filtration rate, *MDRD* modification of diet in renal disease, *CKD-EPI* chronic kidney disease epidemiology collaboration—equation

Hemodynamic and metabolic pathways are involved in the development of DN. Hyperfiltration and hyperperfusion injuries occur very early in DN, and are glomerular hemodynamic changes related to the decrease of arteriolar resistance, more evident on the afferent side, which lead to a rise in glomerular capillary pressure. In addition to hyperglycemia, other factors, such as prostanoids, angiotensin II (ANGII), nitric oxide (NO), atrial natriuretic factor, growth hormone, glucagon, and insulin may be related to the increase in filtration and perfusion. Vascular endothelial growth factor (VEGF) and cytokines such as transforming growth factor- $\beta$  (TGF $\beta$ ) increase NO production and mediate hyperfiltration. Glomerulosclerosis occurs as a result of high intraglomerular pressure, an increase in mesangial cell matrix production and GBM thickening [10, 11].

Hyperglycemia augments the oxidative stress and overproduction of reactive oxygen species (ROS) that stimulate protein kinase C (PKC) pathways, advanced glycosylation end-products (AGE) formation, TGF $\beta$ , and ANG-II [10].

Glucose transporter-1 (GLUT-1) regulates the entry of glucose into the kidney cell and glucose activates the metabolic pathways. Nonenzymatic glycosylation of glucose produces AGE, activates PKC, and accelerates the polyol pathway; hemodynamic changes activate VEGF, TGF $\beta$ , interleukin-1 (IL-1), IL-6, IL-18, and tumor necrosis factor alpha (TNF $\alpha$ ) and together increase albumin permeability in GBM and extracellular matrix accumulation, leading to elevated proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis [11].

Pathologic abnormalities in the kidneys occur before the onset of microalbuminuria. The hallmark of DN is a nodular glomerulosclerosis, the Kimmelstiel-Wilson lesion [12], but less than one-third of diabetic patients with microalbuminuria have the typical glomerulopathy [13]. The earliest changes are an increase in the extracellular matrix and mesangial cell hypertrophy. There is an increased deposition of type IV collagen in GBM, and the thickening may start as early as 1 year after the onset of T1DM, and later in glomerulosclerosis the deposition of collagen



**Fig. 36.1** Kidney alterations of diabetic nephropathy

type 1 and III also occurs. Hyperglycemia impairs integrin expression and the structure and function of the podocytes, which are glomerular epithelial cells that cover the GBM. Hyperglycemia also reduces the number of podocytes, which is related to proteinuria, although this decrease is observed even in the absence of proteinuria and occurs before the development of glomerulosclerosis and tubulointerstitial damage [11] (Fig. 36.2).

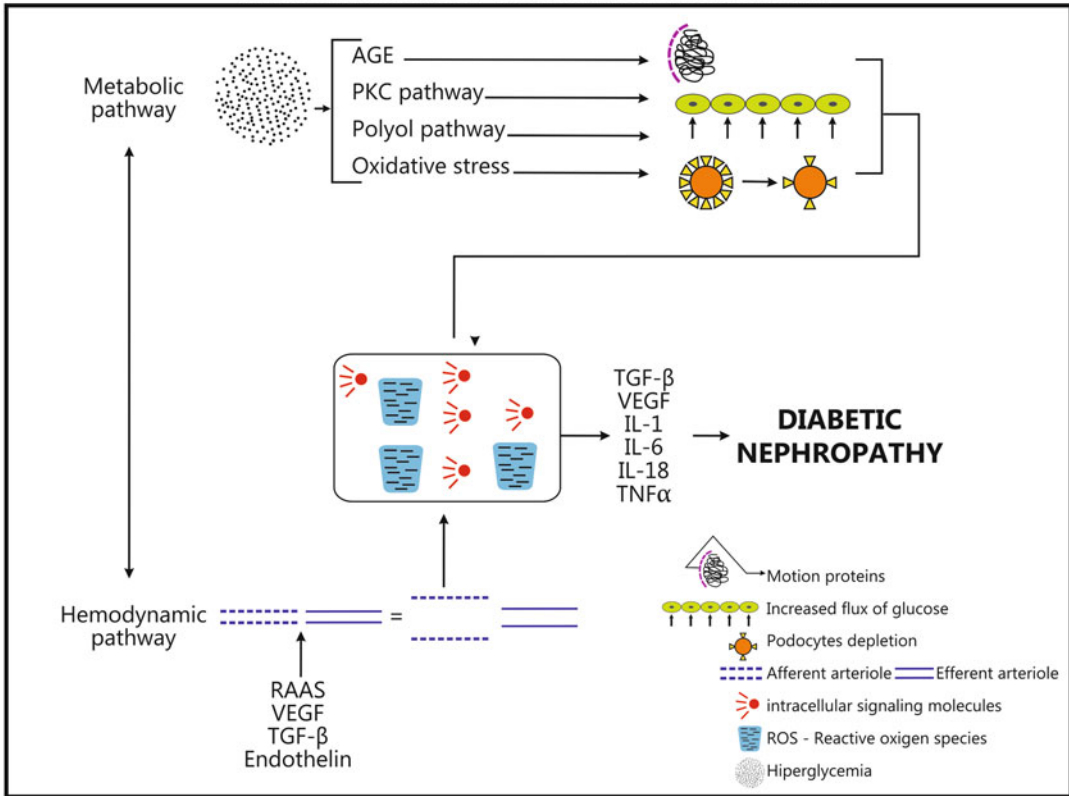
In view of the heterogeneity of kidney lesions and the complexity of the natural history of DN Tervaert et al., in 2010, defined four classes of DN according to the glomerular lesions found on electron microscopy that can be applied in both type 1 and type 2 diabetes [14]. In this classification class I is identified by an isolated GBM thickening (>430 nm in males over 9 years of age and >395 nm in females), with no evidence of mesangial expansion, increased mesangial matrix, or global glomerulosclerosis involving more than 50 % of the glomeruli, and glomeruli lesions then increase progressively to class IV,

which is characterized by advanced diabetic sclerosis. (>50 % global glomerulosclerosis).

The “conventional” natural history of DN was defined in the 1980s, based on longitudinal studies of patients with type 1 and type 2 diabetes, and divided DN into five stages [15] as follows: stage 1 with a reversible glomerular hyperfiltration; stage 2 with normal GFR and normoalbuminuria; stage 3 GFR still normal but associated with microalbuminuria (5–10 years after diagnosis of DM); stage 4, in which proteinuria appears and may reach nephrotic range levels (after 10–20 years of diabetes progression); and stage 5, characterized by a GFR slope below 10 ml/min/year and CKD, leading to ESRD.

Information on the likelihood of passing from one stage to another in newly diagnosed patients was provided by the findings of the United Kingdom Prospective Diabetes Study (UKPDS) [16]. However, the study also emphasized that the risk of mortality increased in parallel with the worsening of renal disease. After 10 years of

**METABOLIC AND HEMODYNAMIC PATHWAYS RELATED TO THE PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY**



**AGE:** Advanced Glycosylation Products; **PKC:** Protein Kinase C; **TGF-β:** Transforming Growth Factor β; **VEGF:** Vascular Endothelial Growth Factor; **IL- 1,6,18** - Interleukin 1,6,18 - **TNFα** - Tumor Necrosis Factor α; **RAAS** - Renin Angiotensin Aldosterone System

**Fig. 36.2** Metabolic and hemodynamic pathways related to the pathophysiology of diabetic nephropathy

diagnosis 25 % of the patients with T2DM developed microalbuminuria and 5 % macroalbuminuria, and in the latter the death rate exceeded the rate of progression to an advanced stage of nephropathy [17].

The Diabetes Control and Complications Trial (DCCT) showed that less than 2 % of patients on intensive treatment developed renal failure after 30 years of diagnosis. The development of microalbuminuria in patients with T1DM usually begins 5–15 years after the onset of diabetes and increases progressively. Patients without proteinuria after 20–25 years have an approximately 1 % per year risk of developing clinical renal disease [9].

Nevertheless, another natural history of DN has been identified, particularly in type 1 and type 2 diabetic patients, although it is not clear why some patients develop the “classical” DN

with significant proteinuria, while others have impaired renal function associated with very low levels of proteinuria that may persist until the ESRD [8, 15].

It would be useful to identify individuals, still normoalbuminuric, whose likelihood of progression to microalbuminuria is increased, but this is not yet possible. In addition to environmental influences, there is evidence in support of genetic susceptibility to microvascular complications of nephropathy in diabetic patients. Earlier investigations that focused on genetic mapping have generally yielded conflicting results, probably because, like other human diseases or syndromes, DN can develop from the interactions of several genes that in isolation would have no effect but which, when subtly altered, could predispose to DN [18].

**Table 36.2** Treatment targets of glycemia, blood pressure, dislipidemia

Glycemic control	HbA1C < 7, <6.5	Caution with patients with advanced kidney disease and high-risk CVD <sup>a</sup>
BP <sup>b</sup> control	<130×80 mmHg	Caution with patients with high-risk CVD
LDL <sup>c</sup>	<100/dl, <70 mg/dl	Stage 5 of kidney disease: start statin only if specific CVD risk

<sup>a</sup>CVD cardiovascular disease<sup>b</sup>BP blood pressure<sup>c</sup>LDL cholesterol low-density lipoprotein

Hence, it is important to enquire about the family history of DN and to screen periodically all diabetic patients. Microalbumin and serum creatinine (SCr) tests are valuable laboratory markers used to detect early signs of kidney damage [4]. A recent study that evaluated the risk stratification of kidney disease emphasized that both the urine microalbumin level and urine albumin/creatinine ratio tests are needed to fully assess kidney disease and its associated risks of death and progression to ESRD [19] (Table 36.2).

“Kidney Disease: Improving Global Outcomes” (KDIGO) conducted a meta-analysis of nine cohorts from the general population and another eight cohorts with a high risk for CKD, which confirmed that lower eGFR and higher albuminuria are risk factors for ESRD, acute kidney injury, and progressive CKD in both the general and high-risk populations, independently of each other and irrespective of cardiovascular risk factors [20].

The gold standard for GFR measurement is urinary clearance of an exogenous filtration marker, which is expensive and troublesome, and in addition to which it varies during the day. In clinical practice SCr is used to estimate GFR, applying the modification of diet in real disease (MDRD) and/or CKD epidemiology collaboration (CKD-EPI) equations [21], which use clinical variables as substitutes for unmeasured non-GFR determinants and provide more accurate estimates than SCr alone. Estimates of the CKD burden depend in part on the equation used to define the eGFR: when the more recent CKD-EPI equation is used, the prevalence of eGFR below 60 ml/min/1.73 m<sup>2</sup>

is lowered by a factor of 0.88 (6.9 versus 7.8 %), compared with the estimate from the older MDRD study equation [4].

In patients with T1DM the first screening is recommended at 5 years after the diagnosis [22], but it is suggested that patients with poor metabolic control be evaluated at the onset of puberty, which is an independent risk factor for microalbuminuria [23]. On the other hand, as about 7 % of the patients with type 2 diabetes will already have microalbuminuria at the time of diagnosis of diabetes, the screening must be started by then. If microalbuminuria is absent, the screening must be repeated annually for both type 1 and 2 diabetic patients [17].

In general, the Medical Societies recommend that an assessment of UAE be performed annually [24, 25], starting at the diagnosis of T2DM and 5 years after that for T1DM, in combination with a measurement of SCr in order to estimate GFR and determine the stage of CKD.

Kidney disease is classified in five stages [24] according to the GFR (ml/min per 1.73 m<sup>2</sup> body surface area), considering kidney damage as abnormalities on pathologic, urine, blood, or imaging tests. Stage 1 is characterized by kidney damage with normal or increased GFR (≥90), stage 2 also by kidney damage associated with mildly decreased GFR (60–89), stage 3 by a moderately decreased GFR (30–59), stage 4 by a severely decreased GFR [15–29], and stage 5 as kidney failure defined as GFR below 15 or dialysis.

In February 2007, a consensus conference in the UK [26] approved the division of stage 3 CKD into stage 3A (eGFR 45–59) and stage 3B (eGFR 30–44) and added the suffix “p” to the GFR-based stage for patients with proteinuria (random urine protein:creatinine ratio >100 mg/mmol). These changes have been endorsed by the National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI). Patients at stages 1–3 are considered to have early CKD.

The measurement of albuminuria may be performed by albumin-to-creatinine ratio (ACR) in a random spot collection, but also in 24-h or timed collections, which are less predictive and accurate

[25]. If albuminuria is abnormal, the test should be confirmed by 2 or 3 samples within 3 or 6 months because albumin excretion may rise due to exercise within 24 h of sampling, infection, fever, congestive heart failure (CHF), marked hyperglycemia, hypercholesterolemia, and high blood pressure.

In the new nomenclature the term microalbuminuria (UAE—30–300 mg/24 h (20–200 µg/min) or ACR—30–300 mg/g) is replaced by “high albuminuria” and macroalbuminuria (UAE  $\geq$ 300 mg/24 h ( $\geq$ 200 µg/min) or ACR  $\geq$ 300 mg/g) by “very high albuminuria,” now recommended because the risk observed between urine ACR and CVD and between the former and renal disease is continuous; there is no specific threshold, and the risk is observed even in those with “high normal” range urine albumin excretion [27]. In addition, the term microalbuminuria does not reflect the amount of albumin, but small albumin molecules, and is becoming increasingly more confusing as a result of new evidence that urine may contain different immunoreactive moieties and fragments of albumin [28].

## Differential Diagnosis

Very often clinicians tend to attribute proteinuria and renal impairment to DM, but that is not the only renal abnormality found in diabetics [29]. Other causes of CKD should be considered in patients that present with an absence of diabetic retinopathy, low or rapidly decreasing GFR, rapidly progressive proteinuria or nephrotic syndrome, refractory hypertension, presence of active urinary sediment, signs or symptoms of other systemic disease or a reduction in GFR of more than 30 % within 2–3 months after starting angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) [24]. Moreover in some patients the DN may be associated with other kidney diseases.

Nondiabetic renal disease (NDRD) includes a heterogeneous mixture of the following glomerular and nonglomerular conditions: [29]

1. Glomerular disease other than diabetic nephropathy: immunoglobulin A nephropathy, focal and segmental glomerular sclerosis,

microvascular complications of diabetes, membranous glomerulonephritis, membranoproliferative glomerulonephritis, pauci immune, systemic lupus erythematosus, and others.

2. Nonglomerular renal disease: macrovascular (renovascular), acute kidney injury (acute interstitial nephritis e.g. contrast nephropathy, sepsis, ACEI/ARBs/direct renin inhibitor (DRI) induced, and acute tubular necrosis e.g. sepsis, diuretic toxicity), electrolyte abnormality, urinary tract infection, etc.

Nevertheless, no consensus classification is available at the moment for kidney biopsy in a diabetic patient with any pathological condition.

## Treatment—(Table 36.2)

Interventions that have been reported to be useful in preventing or retarding the progression of DN include the following: good glycemic and blood pressure control, treatment of hyperlipidemia, cessation of smoking, and restriction of protein intake. Patients who develop ESRD will require renal replacement therapy [30].

Blood pressure and glycemic control represent the major cornerstones for preventing and treating diabetic nephropathy [4, 9]. The DCCT reported that any decrease in hemoglobin A1C (HbA1C) was strongly associated with a reduction in the risk of developing microalbuminuria and progression to overt nephropathy [9], and UKPDS clearly demonstrated a role for intensified glycemic control in subjects newly diagnosed with T2DM, in whom treatment led to a fall in HbA1C from 7.9 to 7.0 % [31].

To reduce the risk or slow the progression of nephropathy the American Diabetes Association (ADA) recommends the optimization of glucose and control of blood pressure. Recently, the ADVANCE study demonstrated that the decrease in HbA1C to a mean of 6.5 % was associated with a further reduction in renal events, as assessed by the development and progression of microalbuminuria [32]. However, the findings of the ACCORD study [33] led to controversy regarding the appropriate HbA1C target for reducing macrovascular disease.



The major risk of reaching HbA1C levels below 7.0 % is the increased likelihood of developing hypoglycemia. For people with decreased kidney function (CKD stages 3–5), hypoglycemia is a major concern because it impairs the clearance of insulin and a number of oral agents used to treat diabetes, as well as reducing kidney gluconeogenesis [24]. Drug adjustments must be made to prevent or, at least, reduce the risk of hypoglycemia.

Sulfonylureas in general have predominantly renal elimination and are not recommended for patients with creatinine clearance (CrCl) below 50 ml/min, except for glypizide, which has hepatic elimination of inactive metabolites and should be interrupted when CrCl falls below 30 ml/min. Malnutrition, acute illness, liver disease, and alcoholism are risk factors for hypoglycemia. Meglitinides are oxidized by the liver but still entail a risk of hypoglycemia because active metabolites may accumulate in renal dysfunction, repaglinide being the one that accumulates the smallest amount of metabolites. Metformin is eliminated unchanged by the kidneys; NKF-KDOQI contraindicated its use with a serum creatinine over 1.5 mg/dl in males and 1.4 mg/dl in women due to the risk of lactic acidosis, although NICE recommends that it should be used with care for patients with an eGFR below 45 ml/min/1.73 m<sup>2</sup> and discontinued if the eGFR falls below 30 ml/min/1.73 m<sup>2</sup>. Acarbose is not recommended if CrCl is below 25 ml/min, and miglitol produces renal elimination, but as there are no studies in patients with kidney disease, FDA do not recommend either of them if serum creatinine is  $\geq 2$  mg/dl. The risk of side effects when using thiazolidinediones increases with renal disease [24, 34].

Exenatide and its formulation with extended release are eliminated by renal filtration and need no adjustment with CrCl above 50 ml/min. Increases in the dosage from 5 to 10  $\mu$ g should be applied with care if CrCl is 30–50 ml/min and, according to FDA, when CrCl is below 30 ml/min it should be stopped. Liraglutide should be used with care when CrCl is below 60 ml/min, and when below 30 ml/min its side effects increase, but experience of its use is still limited in CKD. The dipeptidyl peptidase-4 (DPP4)

inhibitor agents need no adjustment if CrCl  $\geq 50$  ml/min; sitagliptine should be reduced to 50 mg/d if it is 30–50 ml/min and to 25 mg if  $< 30$  and saxagliptine to 2.5 mg if  $< 50$  ml/min. Linagliptine is fecally eliminated unchanged, so it may be safely used in patients with CKD. Colesevalam and bromocriptin need no adjustments. As up to 50 % of insulin is eliminated by the kidney, it is recommended that it be reduced by 25 % when CrCl is 10–50 ml/min and by 50 % if it falls below 10 ml/min [24, 34].

In addition to the importance of glycemic control, it has been shown that a more aggressive BP reduction reduces the progression of DN. The mechanism of hypertension in DN is complex and not fully understood, being related to excessive sodium retention, activation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS), augmented oxidative stress, and endothelial cell dysfunction (ECD) [35].

The UKPDS provided strong evidence that control of BP can slow the development of nephropathy [36]. Treatment using angiotensin-converting enzyme inhibitors (ACEi) retards the progression from micro- to macro-albuminuria and can slow the reduction of the GFR in patients with macroalbuminuria [37, 38]. In T2DM with hypertension and normoalbuminuria, renin-angiotensin system (RAS) inhibition has been shown to delay the onset of microalbuminuria [39, 40]. The evidences suggest that ACE inhibitors [41] have renoprotective actions in addition to their antihypertensive effects for primary prevention [42].

Angiotensin receptor blockers have also been shown to reduce the rate of progression from micro- to macro-albuminuria, as well as ESRD, in patients with T2DM. The Irbesartan in Diabetic Nephropathy Trial (IDNT) [43] and Reduction in Endpoints in noninsulin-dependent diabetes mellitus (NIDDM) study, as well as the Angiotensin Antagonist Losartan (RENAAL) studies, have reported the efficacy of ARBs in nephropathy [33].

The ROADMAP trial investigators evaluated type 2 diabetics with normoalbuminuria and reported that olmesartan was associated with a delayed onset of microalbuminuria, with BP control according to the current standards

(<130×80 mmHg), but there was a higher rate of fatal cardiovascular events with olmesartan among patients with preexisting CVD [40].

It is not known whether the RAS blockade reduced progression to microalbuminuria in normotensive T2DM. Mauer et al. reported that the early blockade of the RAS in patients with T1DM did not slow progression of nephropathy [44].

Furthermore, as it is not yet possible to predict the patients at risk of developing nephropathy, present evidence does not support the use of RAS blockade for the primary prevention of DN [18].

Some reports show that the risk of progressive DN continues to decrease with falls in BP even below the normal range, and such reductions are associated with better clinical outcomes. A recent subanalysis from the BP arm of the ADVANCE study suggested that optimal BP control is less than 125/75 mmHg, particularly in those patients with overt nephropathy [45].

The ideal BP goal in diabetic patients with nephropathy remains questionable, and currently the recommended target is considered to be the same as that for the general diabetic population [46]. An ACE inhibitor or an ARB, usually in combination with a diuretic should be used to treat hypertensive diabetics if CKD is at stages 1–4 with the target of <130/80 mmHg [24].

As the ACEi and ARB are individually renoprotective, questions have arisen regarding the usefulness of combined therapy. The suggestion that a more complete inhibition of angiotensin II, through non-ACE pathways would improve the results stimulated some trials, the older ones, that studied combinations of ACEi and ARB, reported effects that were promising, with significant reductions in albuminuria and/or BP and a good tolerability. Nevertheless, the Candesartan and Lisinoril Microalbuminuria (CALM II) [47] study reported that after 12 months of treatment the effect of the combined therapy was no different from the maximization of each therapy alone in relation to BP or albuminuria. Concerns about this strategy came up with the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [48]. This study tested

patients at high risk for a CV event with an ACEi and/or ARB and observed no differences between groups at the primary endpoint, comprising stroke, myocardial infarction, and sudden cardiac death. However, those patients randomized to combination therapy had higher rates of renal impairment and hyperkalemia, a more rapid decline in eGFR and a greater need for dialysis for acute renal failure episodes during the trial.

Currently, there are no results from large-scale, multicenter randomized trials to support the use of combinations of an ACEi and an ARB in patients with DN. The Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy VA NEPHRON-D Study: Nephropathy in Diabetes Study (VA NEPHRON) study is a multicenter, prospective, randomized parallel group trial testing the efficacy and safety of ACEi (lisinopril)/ARB (losartan) versus ARB on the composite endpoint of reduction in GFR to 30 ml/min (if GFR >60 ml/min), reduction in GFR by 50 % (if GFR <60 ml/min), ESRD, or death in patients with DM2 and nephropathy. The results are expected between 2013 and 2014 and may clarify a number of points [33].

Other drugs, such as diuretics, calcium channel blockers, and  $\beta$ -blockers, should be used as additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs, or as alternative therapy for individuals unable to tolerate those classes of drug. What is generally recommended is the combination of an ACEi or ARB with another class of drug, preferably a diuretic, and calcium channel blockers [24, 37].

ACEi/ARBs are recommended for people with diabetes, proteinuria, CKD, and ACR over 2.5 mg/mmol (men) or 3.5 mg/mmol (women), irrespective of the presence of hypertension or stage of CKD, and should be titrated to the maximum tolerated therapeutic dose before the addition of a second-line agent, with monitoring of the eGFR and serum potassium [37].

The treatment of other comorbidities such as obesity and dyslipidemia should also be considered in patients with DN. Obesity is associated

with glomerular hyperfiltration and an increase in transcapillary hydraulic pressure, hemodynamic changes that may accelerate the development and progression of CKD [38]. Weight loss ameliorates obesity-induced glomerular hyperfiltration and decreases proteinuria, in addition to its beneficial effects on BP and diabetes control [49].

Dyslipidaemia is a risk marker for progressive kidney injury and a risk factor for CVD. However, the evidence that the treatment of dyslipidaemia reduces CKD progression is mostly restricted to post hoc subgroup analyses from large cardiovascular clinical trials, such as the Heart Protection study and the Cholesterol and Recurrent Events (CARE) study. Results from the Study of Heart and Renal Protection trial (SHARP) showed no significant differences in the number of patients with CKD suffering from kidney failure. People with DM and CKD should be treated according to current guidelines for high-risk groups [49].

The target for low-density lipoprotein cholesterol (LDL-C) in people with DM and CKD stages 1–4 should be below 100 mg/dl, but may be considered to be below 70 mg/dl, while patients whose level is above the target should be treated with a statin, which is the preferred therapy [24, 25]. However, a statin should only be started in patients on hemodialysis therapy if there is a specific cardiovascular indication.

No adjustment of dosage is necessary for bile acid sequestrants, niacin, ezetimibe, atorvastatin, or pravastatin. The dosage of rosuvastatin should not exceed 10 mg if CrCl is below 30 ml/min/1.73 m<sup>2</sup> and the patient is not on hemodialysis; it is recommended that simvastatin therapy be started at 5 mg daily in patients with severe kidney disease; daily doses of lovastatin above 20 mg should be used with care if CrCl is below 30 ml/min, while fluvastatin may be used with care in patients with severe kidney disease, but there are no studies using doses greater than 40 mg. The dose of gemfibrozil should be decreased or alternative therapy considered in patients with SCr over 2 mg/dl. Therapy with fenofibrate should be started at 54 mg daily; its effects on kidney function and lipid concentra-

tions should be assessed and the dose reduced in patients with CrCl below 50 ml/min [24].

Smoking has also been shown to increase the risk of progression of CKD to end-stage renal disease (ESRD) irrespective of the primary renal disease; hence the indication is a total cessation of smoking.

A diet therapy with protein restriction is recommended for patients with CKD as it has a great impact on this population. Although dietary protein is limited, adequate caloric intake should be maintained by increasing calories from carbohydrates and/or fats and the qualitative and quantitative aspects of proteins, carbohydrates, and fats should also be taken into consideration. A reduction in protein intake to 0.8–1.0 g/kg body wt/day in individuals at the earlier stages of CKD and below 0.8 g/kg body wt/day at the later stages of CKD may improve the results of renal function as assessed by UAE rate and GFR [24].

The optimal time for initiation of chronic dialysis remains unknown. There is a trend in the nephrology literature toward an earlier initiation of dialysis. However, prospective data that could guide physicians are not yet available [50].

Patients with CKD stage 4 should be referred to a nephrologist. Late nephrology referral before dialysis initiation is associated with increased morbidity and mortality [51].

Kidney transplantation provides high-quality life years for patients with ESRD. The largest numbers of transplants are performed in the United States, China, Brazil, and India, and the countries whose populations have the greatest access to transplantation are Austria, the United States, Croatia, Norway, Portugal, and Spain. However, access to transplantation is still considerably limited across the globe [2].

Guidelines [24, 25] recommend that all patients be evaluated annually with the measurement of creatinine, UAE and potassium, and that those GRF is 45–60 referred to a nephrologist if a nondiabetic kidney disease is suspected. The eGFR should be monitored every 6 months and bicarbonate, hemoglobin, calcium, phosphorus and, parathyroid hormone at least once a year; ensure vitamin D sufficiency and consider bone

density testing due to the relation between nephropathy and bone disease. The need for dose adjustment of medications should be evaluated and the patient referred for diet counseling. If the GFR is 30–44, the eGFR should be monitored every 3 months and electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, and weight every 3–6 months; dose adjustment of medications should be considered, and if GFR is below 30, the patient should be referred to a nephrologist.

Hemoglobin A1C (A1C) remains a widely used and trusted tool for assessing glycemic control in patients without advanced nephropathy or anemia, but there are conflicting data as to what A1C level should be targeted to prevent complications, especially cardiovascular ones, in patients with nephropathy. A lower value of A1C for similar glucose levels is seen in patients with DN than for those without nephropathy. This observation may reflect a shortened erythrocyte survival. The accuracy of the A1C assay is diminished by uremia and unadjusted A1C results are not the optimal assay for patients on hemodialysis or peritoneal dialysis treatment as it may underestimate glycemic control in those patients [24, 52].

It is reported that glycated albumin (GA) more accurately reflects recent glucose control, but it is still necessary to prospectively assess the impact of GA on patient survival and hospitalizations. Freedman et al. reported that for each 5 % increase in GA, the risk of death increased by 14 % in patients under dialysis treatment, and A1C and casual serum glucose did not predict survival. Glycated albumin may be influenced by albuminuria, cirrhosis, thyroid dysfunction, and smoking, and A1C not only by advanced nephropathy but also by a rapid change in diabetes control, severe anemia, hemolytic anemia, iron deficiency, recent blood transfusion, HIV positivity treated with antiretroviral therapy, erythropoietin, and other drugs interacting with erythropoiesis, and chronic alcohol abuse. However, until the GA assay is available, frequent measurements of serum glucose appear more valuable than A1C in patients on dialysis to evaluate glycemic control [52].

## Novel Therapies

The mechanisms involved in injury to the kidney glomerular, interstitial, and vascular functions consist of inflammation, oxidative stress, endothelial dysfunction, and accelerated fibrosis, as described above. Endothelium dysfunction consists of the impairment of many aspects of endothelial functions, including the anti-inflammatory, antiproliferative ones and vasodilatation. Vascular inflammation is a result of a combination of an impaired vasomotor response, an increase in cell proliferation and platelet aggregation, and vascular permeability.

Extensive research is currently underway in this field and several new pathogenic mediators for DN have been discovered, including renin; AGE; PKC; transforming growth factor—Beta 1 (TGF- $\beta$  1); NO; VEGF; and oxidative stress.

Studies have focused on the role of these mediators and possible novel treatments using these approaches, and following new classes of treatment are under investigation: protein kinase C-inhibitor (ruboxistaurin); glycosaminoglycans (sulodexide); AGE formation inhibitors (amino-guanidine, ALT-946, pyridoxamine, thiamine); endothelin receptor antagonist (avosentan.); direct renin inhibitor (aliskiren); AGE breakers (alagebrium, TRC4186); AGE receptor antagonists (endogenous secretory RAGE, RAGE antibody); TGF inhibitors (pirfenidone, SMP-534); connective tissue growth factor (CTGF) inhibitors (anti-CTGF ab); VEGF inhibitors (SU5416); anti-oxidant (curcumin); hemorheologic properties and phosphodiesterase inhibitor (pentoxifiline).

Some of these have yielded promising results in trials, but more clinical studies are still needed to establish their effects on DN, as with aliskiren, pyridoxamin, pentoxifilin, roboxistaurin, pirfenidone and anti-CTGF antibody (Table 36.3).

All the other drugs, despite their promising results in animal model, are not the subject of any current trial. The ASCEND study on avosentan was discontinued due to drug-related adverse events, and initial studies of sulodexide were promising, but a major adequately powered clinical study did not confirm those promising findings [33, 53].

**Table 36.3** Novel drugs for the treatment of diabetic nephropathy with promising results in initial trials

Drug	Class	Action
Aliskiren	Direct renin inhibitor	↓20 % urinary albumin-to-creatinine ratio
Pyridoxamine	AGE <sup>a</sup> formation inhibitors	↓48 % serum creatinine. Do not affect UAE <sup>b</sup>
Pentoxifylline	Hemorheologic phosphodiesterase inhibitor	Antiproteinuric agent
Roboxistaurin	PKC <sup>c</sup> beta inhibitor	↓albuminuria, glomerular and interstitial fibrosis
Pirfenidone, SMP 534	Antifibrotic, TGF-β inhibitors	↓mesangial expansion and fibrosis in animals. Trial results not yet known.
Anti-CTGF <sup>d</sup> antibody	Anti-CTGF therapy	↓ albuminuria

<sup>a</sup>AGE advanced glycosylation end-products

<sup>b</sup>UAE urine albumin excretion

<sup>c</sup>PKC protein kinase C

<sup>d</sup>CTGF connective tissue growth factor

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## Diabetic Foot Ulcerations

Diabetic foot ulcerations (DFUs) are among the most common lower extremity complications, with the lifetime risk of a person with diabetes developing a foot ulcer reported as high as 25 % [1]. Common contributing factors to diabetic foot pathology, including peripheral neuropathy and vascular disease, are reported to be present in more than 10 % of people at the time of their diabetes mellitus diagnosis [2]. Diabetic peripheral neuropathy is the leading cause of DFUs. Both peripheral sensory and autonomic neuropathy that is often found in these patients is related to hyperglycemia. As a result on examination, the patient may present with dry skin or callus and sensory loss noted via monofilament testing. These characteristics combined with a digital or a foot deformity as seen in the setting of motor neuropathy can increase the risk of ulceration in any shoe gear. Trauma in the insensate diabetic

foot can lead to sudden loss of skin integrity such as that seen in foreign body puncture wounds. Patients with advanced diabetic peripheral neuropathy may also exhibit unstable gait patterns and problems with balance, further predisposing them to foot and/or ankle trauma.

Peripheral vascular disease (PVD) is another contributing factor to DFUs, as diabetic patients have a fourfold higher prevalence of atherosclerosis than nondiabetic patients, therefore increasing the risk for decreased lower extremity perfusion [3]. The most common clinical progression of PVD includes claudication, absent peripheral pulses, rest pain, and tissue loss. Although DFUs are often the result of multiple factors, any signs or symptoms of ischemia should be investigated carefully. Noninvasive arterial testing including ankle-brachial indexes, pulse volume recordings, segmental pressures, toe pressures, and transcutaneous oxygen measurements should be performed if pedal pulses cannot be palpated or if arterial insufficiency is otherwise suspected. If major arterial occlusive disease is identified, a vascular surgery consultation is necessary for further assessment and/or revascularization techniques. DFUs in the presence of PVD can rapidly progress to gangrene and/or infection of the entire foot and therefore require prompt attention and treatment. Prophylactic surgical correction of foot deformities such as digital and/or soft tissue contractures can be considered in diabetic patients with well-controlled blood glucose levels and without PVD in order to prevent ulceration.

Although they can occur anywhere in the lower extremity, the most common location for DFUs is

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the forefoot, specifically at the digits and plantar metatarsal heads. The ulceration size and depth of tissue involvement should be carefully assessed to determine the appropriate course of treatment since the severity of the ulceration far outweighs its location with regard to final outcome [4]. Debridement of the ulceration is a crucial step not only for evaluation but also for adequate treatment. Removal of diseased tissue including biofilm at the wound bed can correct cellular abnormalities that impede the normal wound healing sequence in addition to revealing the actual depth and extent of the soft tissue defect. Moreover, reduction of callus tissue can relieve pressure at the site and may be performed in a serial manner. Plain radiographs can assist in evaluating for any underlying osseous involvement, whether it might be deformity or deep infection. Maintenance of a healthy wound environment further requires balancing moisture and decreasing edema, both of which can be addressed through widely available wound care dressings and adjunct hyperbaric oxygen therapy modalities.

Bioengineered soft tissue substitutes may be considered to facilitate healing of small DFUs. Off-loading of the ulceration through surgical shoes/boots, multi-density insoles, splints, and/or casting is imperative to reduce pathologic shear forces and plantar pressures. Glycemic control and healthy nutrition status should be goals for expedited wound healing and prevention of further complications. Even after complete diabetic wound healing has occurred, the patient requires routine surveillance and off-loading measures since the risk of DFU recurrence is high, especially with concomitant neuropathy and/or PVD.

If conventional wound care techniques fail to provide timely healing, surgical wound closure can be a viable option for certain diabetic patients. The mere presence of a lower extremity wound has been documented to significantly extend the length of hospital stay in diabetic patients [5]. A wide variety of surgical options exist to decrease wound duration ranging from primary closure to skin grafting, adjunctive negative pressure wound therapy, and an array of plastic surgical techniques including local random, muscle, or pedicle flaps depending on the characteristics of the given diabetic foot wound. Patients considered

for surgical intervention require medical optimization to decrease the systemic effects of diabetes mellitus that can interfere with wound healing (Fig. 37.1).

Surgical off-loading with the utilization of external fixation can provide a stable construct that will protect any soft tissue reconstruction during the postoperative period. This method allows access to the surgical flap site for postoperative care and also aids in encouraging non-weight-bearing status for the recovery period if necessary. Careful patient selection with an appropriate rehabilitation regimen is paramount to avoid any inherent complications associated with reconstructive surgery in the diabetic population (Fig. 37.2).

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## Diabetic Foot Infections and Amputations

Diabetic foot infections (DFIs) account for the largest number of diabetes-related hospital days and are the most common cause of non-traumatic lower extremity amputations [6, 7]. Many of the risk factors for DFUs also serve as the risk factors for DFIs, with diabetic neuropathy, PVD, and immunopathy having the most apparent influence. Hyperglycemia has a role in impairing the diabetic patient's immune system through abnormalities in leukocyte function and changes in macrophage morphology. A pathologic cycle is created since elevated glucose levels inhibit the host's defense to DFIs, while the presence of infection further affects glycemic control.

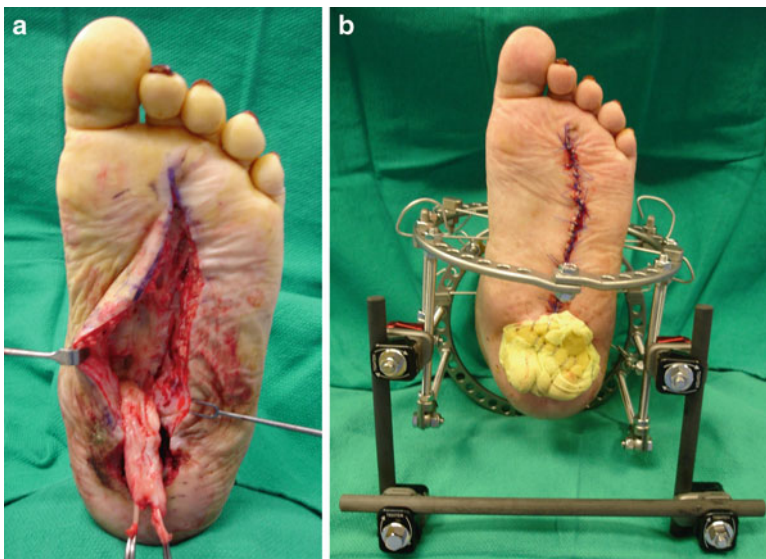
DFIs are diagnosed through a thorough history and physical examination, and confirmation can be made through laboratory testing and diagnostic imaging. The Infectious Diseases Society of America (IDSA) has defined the presence of infection as  $\geq 2$  classic findings of inflammation (purulence, erythema, warmth, pain, or induration) [8]. Local debridement and probing of the wound can help determine the severity and extent. Hospitalization and antibiotic therapy can be determined based on the IDSA category of clinical infection: mild (superficial and limited in size and depth), moderate (deeper or more extensive), or severe (accompanied by systemic signs





**Fig. 37.1** Preoperative clinical picture (a) of a severe diabetic foot infection including multiple anatomic compartments that required initial urgent surgical debridement followed by a revisional surgery with the use of negative-pressure wound therapy

(b, c). The patient was followed closely in the postoperative period with frequent visits to a wound care clinic as well as further reconstruction with biological dressings (d) and autogenous split thickness skin grafting (e)



**Fig. 37.2** Intraoperative clinical picture of a local flexor digitorum muscle flap (a) for coverage of a plantar central diabetic foot ulceration due to Charcot neuroarthropathy.

Note the surgical off-loading by utilizing an external fixation device for postoperative care and non-weight-bearing status (b)

of metabolic perturbations). As mentioned before, depending of the extent of the wound and infection, plain radiographs should be initially utilized to detect the presence of osteomyelitis and soft tissue emphysema. Magnetic resonance imaging (MRI) can provide information to help differentiate abscess, osteomyelitis, and neuropathic arthropathy.

Evidence of systemic toxicity (fever and leukocytosis), metabolic derangement, progressive deep soft tissue infection, gangrene, or the presence of critical ischemia warrants immediate hospitalization. Initial laboratory testing including complete blood count, metabolic profile, inflammatory markers, and hemoglobin A1C is important to establish a baseline and monitor response to treatment. Medical stabilization to correct electrolyte imbalance and control blood glucose levels is important prior to surgical intervention. Consultation with other services such as internal medicine, nephrology, endocrinology, infectious disease, and cardiology is determined based on the patient's medical co-morbidities.

Empiric intravenous antibiotics may be started until reliable intraoperative deep cultures and bone biopsy when indicated are obtained to determine appropriate antibiotic therapy. Although most DFIs have been reported as polymicrobial, the most commonly isolated organisms are *Staphylococcus* and *Streptococcus* species [8]. Prior hospitalization and previous history of osteomyelitis increase the risk for infection by emerging multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Surgical intervention should be initiated for early and aggressive debridement of the acutely infected diabetic foot with further recommendations for antibiotic treatment by the infectious disease team.

DFIs can have different manifestations such as local or extending cellulitis, abscess formation, gangrene, necrotizing fasciitis, and osteomyelitis. Isolated localized cellulitis can be treated via antibiotic therapy, whereas the other infectious pathologies necessitate adequate surgical debridement. Abscess formation can be addressed through incision and drainage with resection of

adjacent nonviable tissues. Gangrenous tissue which results from local ischemia induced by acute bacterial toxicity should be sharply debrided and limb-threatening infections such as necrotizing fasciitis require emergent surgical debridement. Treatment options for osteomyelitis documented in the literature include antibiotics with or without surgical excision. Depending on the extent, such as in cases of joint sepsis or involvement of multiple anatomic foot compartments, a partial foot amputation may be required.

Surgical incision placement should take into account the angiosomes of the foot and ankle in order to preserve optimal vascularity [9]. If a minor foot amputation is required, the level of viable soft tissue and bone combined with the level of healthy perfusion should help guide the level of amputation. Multiple surgical debridements may be often necessary to adequately resolve the infection and produce a healthy granular wound that can be considered for future soft tissue reconstruction. Staged surgical procedures using local antibiotic delivery systems in the form of beads or spacers can be used to produce an infection-free yet mechanically stable environment for delayed reconstruction [10]. Major amputation may play a role in cases where infection involves the entire foot and is extending proximally to the leg or when arterial perfusion is not sufficient for diabetic limb salvage despite efforts for revascularization. Rehabilitation following an amputation can be facilitated by physical and occupational therapy services at home or in skilled nursing facilities if necessary. After surgical debridement and/or amputation, continued medical management, patient education, counseling, and postoperative care should be maintained in order to achieve long-term prevention of further complications.

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### Diabetic Charcot Foot Neuroarthropathy

Charcot neuroarthropathy (CN) is a complication of diabetic peripheral neuropathy that involves progressive fractures and/or dislocations that result in severe foot and ankle deformities caus-

ing potential for skin ulceration and infection. Diabetes mellitus is the leading cause of CN in the western world and each diabetic patient should be screened and educated about the risk of this debilitating condition [11]. The ideal situation in the subacute or acute stages of diabetic CN is to initially immobilize the patient and further protect the affected areas with appropriate custom bracing to prevent any related CN complications. Even with the early recognition of CN, certain deformities are not amenable to conservative treatment and require surgical reconstruction to establish a limb that is braceable, functional, and non-ulcerated. Continuous patient education about their loss of protective sensation and devastating complications of CN is essential to avoid a potential leg amputation. Close monitoring of this population with proper medical and surgical intervention when necessary is crucial for the overall patient's successful outcome.

Health care providers must have a high index of clinical suspicion for the diagnosis of CN when the diabetic neuropathic patient initially presents with a warm and swollen unilateral lower extremity. Plain radiographs of the foot and ankle need to be obtained but lack of radiographic changes during the initial stages of CN does not exclude the diagnosis. MRI and bone scintigraphy have been shown to be more sensitive in detecting subacute to early acute CN [12]. Often, clinical observation along with repeated plain radiographs is required to determine the need for further immobilization and protective weight-bearing if CN is suspected. If there is concern for a deep space infection and/or deep venous thrombosis, the diagnosis and treatment for these conditions can be carried out accordingly. Often, the erythema associated with CN typically dissipates with bed rest and elevation of the lower extremity whereas the erythema associated with cellulitis and/or infection will remain. In addition, laboratory findings may offer little insight into differentiating diabetic CN from infection in the severely immunocompromised patient.

The clinical stages of CN are categorized into subacute, acute, coalescent, and remodeling [13]. Both subacute and acute CN present with associated erythema, edema, and warmth. A loss of sympathetic response and bounding pedal pulses

may be evident among the early stages of CN. In acute CN, fractures and/or joint subluxations/dislocations are evident on plain radiographs whereas in the subacute stage radiographs are normal. The coalescent stage is marked by decreased edema, erythema, and warmth as it represents bone and joint deformities that resulted from the progression of CN during the acute stage. While the coalescent stage of CN reflects a cessation of the inflammatory process, the fracture pattern may be still unstable and prone to further deformity with weight-bearing status and eventual ulceration. The remodeling stage is categorized by a healing of fractures and consolidation across affected joints. At this stage, the associated CN foot and ankle deformities are more rigid and stable and may be better suited for custom foot orthosis and/or bracing to prevent ulceration.

On the other hand, the ulcerated diabetic CN foot and/or ankle deformity can present with or without infection and poses even greater risk for leg amputation [14]. Ulcerations associated with CN vary depending on the location, depth, underlying deformity, infection, and vascularity. Severe DFIs associated with CN are serious and can be limb or life threatening in cases of hemodynamically unstable patients with significant hyperglycemia and multi-organ failure. The presence of fever, chills, and leukocytosis are not always evident and often severe hyperglycemia may be the only systemic manifestation present with a diabetic limb-threatening infection. Patients require hospitalization and coordination of both medical and surgical disciplines to appropriately expedite the care of this condition. When surgery is performed, collection of soft tissue and bone cultures along with bone biopsy is required to guide antibiotic therapy by the infectious disease team.

The presence of sepsis and deep space infection is the leading cause of amputation among diabetic patients with CN. Surgery to manage the deep space infection in these case scenarios is focused on meticulous and thorough surgical debridement with wide surgical resection of the infected soft tissue and bone segments. Large segmental bone defects can be first addressed by the utilization of local antibiotic beads, rods, and/or spacers to provide a local concentration of antibiotics while



**Fig. 37.3** Preoperative radiographic ankle views (**a**, **b**) showing infected hardware with nonunion at multiple hindfoot and ankle joints of a previously attempted pantalar arthrodesis. Patient underwent removal of the retained internal fixation hardware combined with a total talemectomy, debridement and reaming of the entire tibia medullary canal, insertion of a temporary antibiotic-impregnated large-diameter Steinmann pin and beads at the ankle level,

and a stabilizing off-loading circular external fixator (**c**). Subsequent removal of the antibiotic-impregnated pin and beads with a definitive tibio-calcaneal arthrodesis by modifying the preexisting circular external fixator was performed at approximately 6 weeks after the initial operation (**d**, **e**). Final radiographic ankle views (**f**, **g**) at 6 months' follow-up showing the realignment and successful arthrodesis

simultaneously managing and stabilizing the resected osteomyelitic osseous defects. External fixators are commonly utilized to provide further stability to the foot and ankle as internal fixation is contraindicated in the presence of ongoing infection. External fixation devices can also be applied temporarily to stabilize various segmental osseous defects and major deformities while further surgi-

cal and medical management of the infection is undertaken [15] (Fig. 37.3).

Furthermore, vascular examination and vascular consultation are required if arterial insufficiency is present to determine if further diagnostic testing and/or revascularization is needed prior to future delayed reconstructive procedures. The majority of patients present with chronic diabetic

CN deformities and the presence of peripheral arterial disease may be prevalent in this population in contrast to most of the cases in the acute CN stages where bounding pedal pulses are found due to an altered sympathetic nervous system response.

Patients with diabetic CN may require extensive reconstructive foot and ankle surgery if limb salvage is attempted. Surgical procedures directed to address diabetic CN vary depending on the presence of soft tissue loss, infection, and/or arterial insufficiency in conjunction with the location and degree of the associated deformity. Deformity correction involves joint realignment and arthrodesis procedures at the midfoot, rearfoot, and/or ankle level with either internal and/or external fixation [15]. Internal fixation can be utilized in select CN foot and ankle deformities without ulceration or infection. External fixation is utilized for diabetic CN deformities with a poor soft tissue envelope, ulceration, and/or infection [16]. In selected patients, a plantar foot exostectomy and wound closure may be sufficient for addressing the chronic ulceration associated with a stable Charcot deformity. Finally, close postoperative monitoring of the reconstructed patient with appropriate orthosis/bracing is crucial in order to avoid any future complications.

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## Conclusion

DFIs are responsible for one of the most common reasons of hospitalizations in the diabetic population. A multidisciplinary team effort in the prevention and treatment of the diabetic foot may provide this patient population with increased options to avoid a lower extremity amputation.

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## Introduction

Diabetic retinopathy (DR) is a chronic microvascular complication. It is characterized by progressive changes in the retinal microvasculature leading to areas of non-perfusion retina, increased vascular permeability, and intraocular pathological proliferation of retinal vessels. Complications associated with increased vascular permeability, called macular edema, and uncontrolled neovascularization, named proliferative diabetic retinopathy (PDR), can result in serious and permanent vision loss [1–4].

The pathogenesis of DR is associated with characteristics of both microvascular occlusion and leakage. Hyperglycemia seems to start a cascade of vascular events such as capillaropathy and hematological disorders that lead to a decreased blood flow and microvascular occlusion, resulting in non-capillary perfusion and retinal hypoxia which can cause arteriovenous

shunts between arterioles and venules, known as intraretinal microvascular abnormalities (IRMA) and neovascularization caused by angiogenic growth factors [5–9].

The DR affects 99 % of patients with diabetes mellitus (DM) type 1 and 60 % of patients with type 2 within 20 years of disease, according to the Wisconsin Epidemiologic of Diabetic Retinopathy Study [10–13]. The National Health and Nutrition Examination Survey III of type 2 DM showed that the frequency of DR was higher among non-Hispanic blacks (27 %) and Mexican Americans (33 %) than among non-Hispanic whites (18 %) [14].

Ten years ago, around 170 million people were estimated to have DM, and more than 5 million became blind owing to DR. This number is expected to double worldwide before 2030 [15, 16]. Despite decades of research, there is currently no known method to prevent diabetic retinopathy, except the strict control of blood glucose. The DR is the second leading cause of legal blindness in industrialized countries, only behind age-related macular degeneration. However, if we consider the population between 20 and 74 years of age, DR is the main cause of blindness. Among the 5.8 million known diabetics in the USA, 62,400 (1.07 %) will develop each year the proliferative form of DR, and 75,400 (1.3 %) will present macular edema with poor visual acuity [17–20].

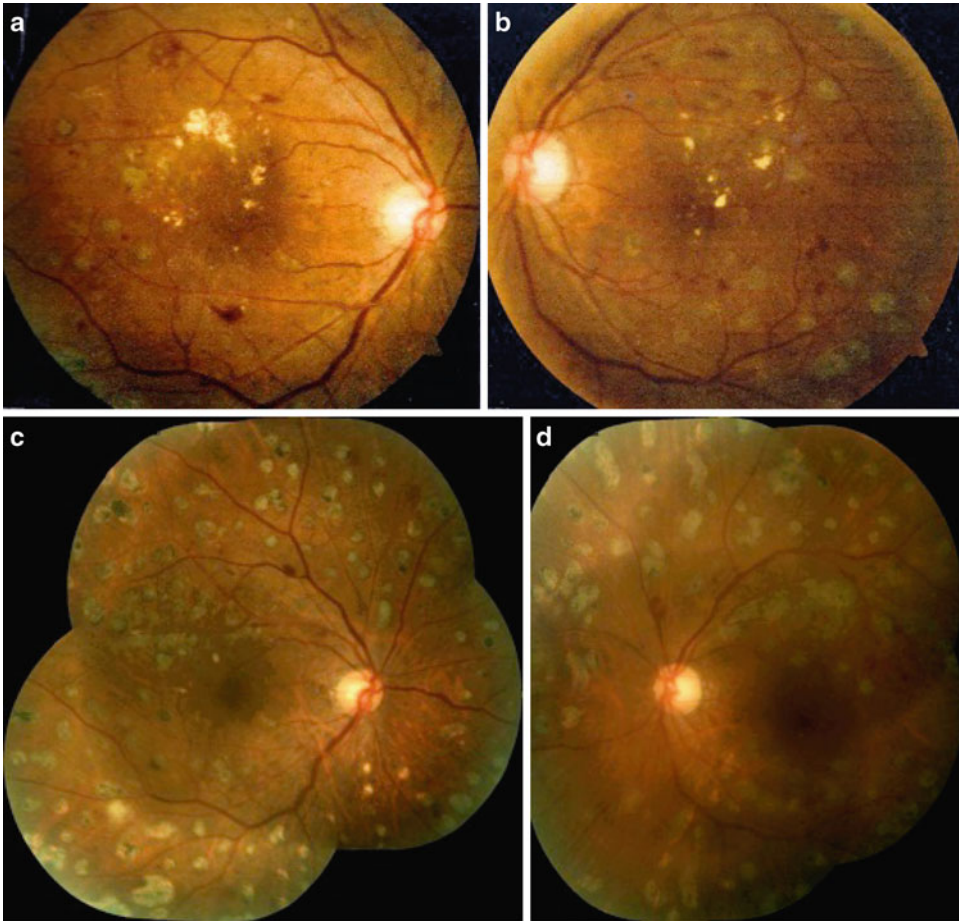
An estimated 700,000 people in the USA have PDR, 130,000 have high-risk PDR, 500,000 have macular edema, and 325,000 have clinically

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**Fig. 38.1** Female, Asian, 68 years old, type 2 diabetes for at least 15 years, visual acuity: 20/400 OD and 20/200 OS. The dilated eye exam revealed clinically significant diabetic macular edema (CSME) OD >OS. Fundus color picture, OD(A) and OS(B) on the first visit (note the hemorrhages, few LASER spots, and posterior pole hard exudates—CSME). Fundus color, OD(C) and OS(D) after 10 months of treatment (note the absence of hemorrhages and hard

exudates and more LASER scars). Baseline OCT OD(E1) (note the central retina diabetic edema); OCT OD(E2) after one intravitreal Ranibizumab injection; OCT OD(E3) after six Ranibizumab injections (note the normal anatomy aspect). Baseline OCT OS(F1) and OCT OS(F2) after one intravitreal Ranibizumab injection, OCT OS(F3) after three Ranibizumab injections (note the normal anatomy aspect). Final vision after 10 months was 20/40 for both eyes

significant macular edema (CSME). Blindness was estimated to be 25 times more common in people with DM than in those without the disease [17–24] (Fig. 38.1).

It is estimated, in another study, that each year 63,000 new cases of PDR arise in the USA, among these 29,000 cases of high-risk PDR. Regarding macular edema, 80,000 new cases are expected, 56,000 being cases of CSME, and 12,000–24,000 new cases of legal blindness occur each year as a result of DR [17, 19, 24].

The Diabetes Control and Complications Trial (DCCT) showed that the rates of DR development and progression were significantly reduced after 3 years of intensive insulin therapy. The effect of reducing the HbA1c from 9.1 to 7.3 % resulted in benefit maintained through the 7 years of follow-up. The progression rate to complications at the end of the DCCT remained lower in the intensive treatment group, although the costs of intensive care are three times the values of conventional therapy [17, 25–28].

**Table 38.1** Diabetic retinopathy classification [29–32]

Nonproliferative diabetic retinopathy (NPDR)	
Mild	At least one microaneurysm or mild level of microaneurysms and retinal hemorrhage
Moderate	Moderate level of microaneurysms and retinal hemorrhage and/or mild levels of cotton wool spots, venous beading, and IRMA
Severe	Severe intraretinal hemorrhages and microaneurysms in all four quadrants, and/or venous beading in two or more quadrants, and/or moderate IRMA in at least one quadrant
Proliferative diabetic retinopathy (PDR)	
Early	NVD or NVE, less severe than high-risk PDR
High risk	NVD $\geq 1/3$ optic disc area, any NVD with vitreous hemorrhage, and/or NVE $\geq 1/2$ optic disc area and preretinal or vitreous hemorrhage
Advanced	Posterior fundus obscured by preretinal or vitreous hemorrhage or center of macula detached
Clinically significant macular edema (CSME)	Retinal edema located at or within 500 $\mu\text{m}$ of the center of the macula
	Hard exudates at or within 500 $\mu\text{m}$ of the center with thickening of adjacent retina
	A zone of thickening larger than one optic disc area if located within one disc diameter of the center of the macula

Abbreviations: *IRMA* intraretinal microvascular abnormalities, *NVD* neovascularization of the disc, *NVE* neovascularization elsewhere

Nevertheless, with appropriate medical and ophthalmologic assistance, over 90 % of visual loss cases resulting from the PDR could be prevented. Therefore, until DM cure is discovered, the emphasis should be on clinical care to prevent vision loss, early diagnosis, correct classification (Table 38.1), and appropriate treatment [29–33].

## Key Points to the Diagnosis

Because DR has few symptoms until vision loss develops, regular screening is critical. A complete ocular evaluation by a retina specialist ophthalmologist is mandatory to diagnose and treat the DR [34, 35].

During the exam the ophthalmologist will test the vision, take eye pressure measurements and

under dilated eye exam—the best way to diagnosed DR, the following will be checked: presence of a cataract, abnormal blood vessels, retina swelling, blood or fatty deposits (hard or soft exudates) in the retina, new blood vessel growth, scar tissue, optic nerve abnormalities, vitreous hemorrhage, vitreoretinal tractions, and retinal detachment [35].

Ancillary tests may be useful to achieve a correct diagnosis and treatment plan, for example the fluorescein angiography (FA) and the optical coherence tomography (OCT).

The FA consists in a sequence of, nowadays, digital picture frames before and after a venous dye (fluorescein) injection. FA is especially useful in the management of DR because it provides information on the retinal circulation and on the status of the blood-retinal barrier. FA is also important to determine the degree of ischemia or the presence of retinal vascular abnormalities [36–38].

OCT, also called “optical biopsy,” is an imaging technique that produces high-resolution cross-sectional images of the retina; the “in vivo slide” shows the thickness of the retina and its layer details. FA and OCT exams are used during the follow-up to monitor how treatment is working as well [36–38].

## Differential Diagnosis

Diagnosing DR is the daily work of the retinal specialty. However it is necessary to consider other etiologies in the differential diagnosis, especially in the presence of a negative work-up for diabetes.

The DR is the most common retinal vascular disease and its differential diagnosis must be made with other ocular vascular disorders such as hypertensive retinopathy, central or branch retinal vein occlusion, arterial occlusive disease, vasculitis, macroaneurysm, other types of macular edema, hemoglobinopathies, retinal telangiectasias, sickle cell disease, valsalva retinopathy, radiation retinopathy, ocular ischemic syndrome, Terson syndrome, and Purtscher retinopathy.

Other less frequent conditions need to be investigated as well in some individuals such as



infectious etiologies (e.g., HIV, CM), inflammatory and autoimmune diseases (e.g., lupus erythematosus), cancer and paraneoplastic retinopathies (e.g., leukemia, lymphoma), muscular dystrophies, phakomatoses, and toxicity (e.g., some drugs) among others.

## Present and Future Therapies

The appropriate clinical management of diabetic retinopathy was defined by the results of several large randomized clinical trials. These studies have elucidated the DR progression rates, follow-up intervals, and effectiveness of glycemic control and laser photocoagulation, considered the golden standard treatment. They also established recommendations for vitrectomy surgery [39–43].

The presence of CSME and high-risk PDR is an indication for immediate treatment. The first treatment option is the LASER; focal or grid LASER is used for macular edema and a panretinal photocoagulation is performed for high-risk PDR cases. Vitrectomy surgery will probably be the choice in cases of PDR associated with tractional and/or rhegmatogenous retinal detachment and long-standing vitreous hemorrhage, where posterior pole retina visualization is poor [39–43].

Considerable progress has been made in the delivery of ophthalmological care for DR over the past decade [44]. Regarding how to perform LASER treatment, great changes have happened such as new LASER wavelengths, pattern scan laser photocoagulator devices, better-view systems, micropulse LASERs, and computer-guided navigated retinal photocoagulation delivery [45, 46].

In recent years, important advances in pharmacotherapy have shown promising results in the treatment of DR, such as the corticosteroids in special triamcinolone acetonide, the vascular endothelial growth factor (VEGF) antagonists—specially the FDA-approved Ranibizumab (Lucentis<sup>®</sup>, Genentech, Inc.), Bevacizumab (Avastin<sup>®</sup>, Genentech Inc.), and Aflibercept (EYLEA<sup>®</sup>, Regeneron Pharmaceuticals, Inc. and Bayer HealthCare Pharmaceuticals), and some other drugs like Infliximab (Remicade<sup>®</sup>, Centocor), Etanercept (Enbrel<sup>®</sup>, Amgen, Inc. and Wyeth), Vitrase (hyaluronidase ovine, ISTA

Pharmaceuticals, Inc.), Octreotide (Sandostatin<sup>®</sup>, Novartis), and Ruboxistaurin (Arxxant<sup>®</sup>, Eli Lilly and Company), among others [47–52].

In conclusion, the DR prevention relies initially in the treatment or the cure of the underlying disease, DM, but it remains a challenge to medicine. However, a strict control of glucose levels should be the primary concern. Once installed the DR complications “a war starts” and action is required; laser therapy and some drugs, if indicated, are the weapons to be used in order to preserve the best possible visual acuity.

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Conceição Chaves

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## What Is Carbohydrate Counting?

It is a tool to help diabetics program their intake of food, by means of which the amount of carbohydrate prescribed is what will define the amount of regular or ultrafast insulin necessary for the meal recommended by the dietitian specializing in diabetes. Thus, besides adapting the dose to individual sensitivity, glycemic control is optimized through the counting of carbohydrates.

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## Who Should Do Carbohydrate Counting?

Counting carbohydrates is a useful tool when setting the diabetic's diet. If we started by asking who should do carbohydrate counting we would come to the conclusion that it is important that all diabetics should do so. If today, those who use only diet therapy to control blood sugar consume, for example, 60 g of carbohydrates at breakfast and double that amount for the same meal at weekends, their glucose levels will rise. Those

who also make use of oral hypoglycemic agents in a quantity that does not vary from the medication, but which alters their consumption of carbohydrates, will suffer from hyperglycemia on the days that they consume more carbohydrates.

Currently there are two schemes of insulinization: the conventional one, using two applications per day of prolonged action insulin, 2/3 of the dose in the morning and 1/3 before dinner or at bedtime, and an intensive one that uses long-acting insulin, representing the basal dose, along with the rapid-acting (regular) or ultrarapid (UR) insulin, both of which should be applied before the meal in question.

In the conventional scheme, since the insulin doses are fixed, the amount of carbohydrates should not vary from day to day. Both insulin therapy schemes require carbohydrates to be counted, thus establishing its importance for the entire population of diabetics. Classical studies such as the *Diabetes Control and Complications Trial DCCT* [1] and *Prospective Diabetes Study Group UKPDS* [2] pointed out that glycemic control, including glycated hemoglobin A1c in the latter, modifies the risk of complications arising from the disease. Therapy that uses counting has been used in Europe since 1930, and in 1990 it was also used in the DCCT study. In 2011 [3], the International Diabetes Federation (IDF) confirmed its view that postprandial hyperglycemia is associated with an increase in retinopathy, oxidative stress, inflammation, and endothelial dysfunction, and thus contributes significantly to cardiovascular risk.

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## Criteria for Prescribing the Counting of Carbohydrates

In type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes, the criteria should be directed at individualizing the diet, achieving the appropriate glycemic goal, and evaluating the time of greatest resistance to insulin. It might be thought that since glycated hemoglobin A1c is verified, self-monitoring should be discarded, but the test for glycated hemoglobin A1c does not evaluate fluctuations in blood glucose levels, besides which it is of fundamental importance that the multidisciplinary team know the glucose levels before and after meals, and especially that they attach due significance to postprandial blood sugar because of its clinical relevance [4]. In type 1 diabetics, the postprandial glycemic target is broader so as to avoid the risks of hypoglycemia generating repercussions for the growth of children and adolescents, but it should be assessed case by case.

Some diabetologists and the American Diabetes Association (ADA) currently consider that between 150 and 180 mg/dl is appropriate. The glycemic level of this population is more difficult to control as one needs to take into account the patient's age, maturity, acceptance of the disease, the concentration of growth hormone, etc. A recently published study involving type 1 diabetics and their families emphasizes the importance of carbohydrate counting in this population. For type 2 diabetics, the goals are more restricted: HbA1c less than 6.5 %, preprandial glucose of 5.5 mmol/( $<100$  mg/dL), and postprandial glucose of 7.8 mmol/( $<140$  mg/dL) IDF [3], 2011. The importance of the entire population of diabetics conducting self-monitoring is emphasized [5]. In gestational diabetes, the biochemical parameters are fasting glucose  $<90$  mg/dL and postprandial blood sugar  $<140$  mg/dL at 1 h and  $<120$  mg/dL at 2 h.

The IDF considers that there is a substantial amount of scientific evidence to suggest that diets with a low glycemic load are beneficial for controlling postprandial glucose. The glycemic load is the glycemic index per edible portion of food; in other words, it is an objective way of expressing to what extent the food content modifies the postprandial response [6].

## Choice of Nutritional Therapy

To control blood sugar with nutritional therapy, there is the exchange list [6, 7] or a list of exchanges representing an average of foods, in which the foods are represented by groups. Available software programs may also be included, such as Diet-Pro or Diet-Win or other programs that analyze diet. This will be calculated by the nutritionist, who will inform the patient of the substitutions to be made.

Another technique is to use foods in isolation. This is a more precise method, and is the most suitable technique for patients who have most difficulty in exercising control, although it is harder to work with. The counting of points is a dietary program that only includes food calories, so it is not recommended.

Another important tool for patients is the manual for counting carbohydrates, which presents food items in isolation, with their amounts of calories and carbohydrates. Then there are pocket manuals that facilitate the calculation of counting, and which present food in household measurements. For patients who use an insulin pump, counting each food item is a better option because their sensitivity to glycemia is greater than the impact of each food item on glycemia. Despite the availability of these methods, the support of the professional dietitian is an important and irreplaceable part of the program of carbohydrate counting [8].

## Action of Insulins

Carbohydrate counting has become a necessity since the advent of ultrarapid insulin analogues. Since 2002 [7], the ADA has advised that it is the amount of carbohydrates in the meal that will define the amount of UR insulin. Indeed, the freedom to eat outside the home has increased with these insulins [9]. It is important to realize that the onset of the action of UR insulin takes 10–15 min and that it should be taken as soon as the individual has defined how much carbohydrate he/she will consume during the meal.

Long-acting insulin will maintain the basal blood sugar and will already have been

prescribed by physician. The amount of ultrarapid insulin required by the meal in question should be that recommended by a nutritionist specializing in diabetes, since it is based on the consumption prescribed by the nutritionist with the participation of the physician. The long-acting insulin regimen, together with UR action insulin, represents the most physiological regimen currently in existence [8, 10].

When the patient makes use of regular insulin, the onset action of which takes 30–60 min and lasts up to 6 h, physicians usually order it to be taken in the morning and in the afternoon; they avoid prescribing it at lunch time because of the risk of hypoglycemia, due to its long action, unless the individual is very resistant to the action of insulin, is very gluttonous, or maintains higher glucose levels after lunch.

It is also important to note that regular or UR insulins correct blood glucose levels which, when high, are known as correction boluses [10]. The improvement in glycemic control is due to the correction of blood sugar levels, by means of individualized observation [11]. For this to happen, it is important to know the sensitivity factor (SF) [11], which varies with the type of insulin. There is a practical rule for checking SF for UR insulin, in which the total dose of insulin/day (basal insulin plus the ultrarapid doses) is divided by the absolute number 1800 [12]. The same applies to rapid insulin, except that the total dose is divided by 1,500. It can be observed that on average 1 unit of UR insulin reduces the level by 45–50 mg/dL and that 1 unit of regular insulin decreases it on average by 25–30 mg/dL. Since we are dealing with individual persons, the peculiarities inherent in each individual require that the observation be made by a multidisciplinary team.

The period of greatest resistance to insulin is in the morning, owing probably to the circadian action of hormones. It may be assumed that patients with kidney disease and the elderly, because of renal dysfunction and their living longer, present a slower insulin depuration rate, and thus require their blood glucose to be monitored more closely because of the risk of hypoglycemia due to the fact that circulating insulin has a

**Table 39.1** Estimate of the insulin:carbohydrate ratio as per body weight

Weight (kg)	Units of insulin:g of CHO
25	1:30
45–49	1:16
49.5–58	1:15
58.5–62.5	1:14
63–67	1:13
67.5–76	1:12
76.5–80.5	1:11
81–85	1:10
85.5–89.5	1:9
90–98.5	1:8
99–107.5	1:7
≥108	1:6

longer life. The concomitant evaluation of their nutritional status is necessary because, when the patient's decompensation improves, his/her weight may go up, which favors greater resistance to insulin [12, 13].

The Dose Adjustment for Normal Eating (DAFNE) study [14], which is used throughout England as a guide in the counting of carbohydrates, when the patient, along with the multidisciplinary team, practices optimizing the amount of insulin to the carbohydrates of the meal, has shown that there is an improvement in the quality of life and glycemic control when such an effective intensive scheme is employed.

The insulin-to-carbohydrates ratio is dependent on the individualized response and uses weight as a reference (Table 39.1). Excess weight increases insulin resistance, as is amply demonstrated in the literature [13]. The higher the weight, the more insulin the individual will take, thus increasing the risk of gaining weight, constituting a vicious cycle. Infections also prompt a rise in glucose levels, which is prevalent in this population.

With regard to children and adolescents, since a child's weight is half that of an adult, 1 unit for every 30 g of carbohydrates is taken, if the child weighs on average 25 kg. Another aspect to be considered is that due to the action of the growth hormone present in children and adolescents, there is greater resistance to insulin, which makes control in this type 1 diabetic population difficult. Individualized and monitored action to evaluate

pre- and postprandial blood glucose levels should be a priority when overseeing the adjustment of the doses of insulin [12, 15].

Another important aspect of glycemic control for those who use insulin therapy is to choose the appropriate insulin needle, which needs to reach the subcutaneous tissue; if the needle is oriented incorrectly, it will make all glycemic control difficult, even if carbohydrate counting is done satisfactorily.

### Exercises

Physical activity is an important pillar in the control of blood glucose because it enhances insulin sensitivity and control of weight [11, 16]. Excessive exercise can elevate blood sugar levels or foster the emergence of hypoglycemia. Decompensated patients should only start exercise after their glucose levels have been adjusted because of the action of counter-regulatory hormones.

### What Is the Effect of Alcohol on Blood Glucose?

Alcohol has 7 cal for 1 g. It is metabolized, enters the Krebs cycle, and provides energy, referred to as empty calories, because it contains neither vitamins nor mineral salts. Starting at 15 g of ethanol for women and 30 g for men, there will be an increase in blood pressure and glucose levels; 30 g of ethanol is the equivalent of two shots of whisky, two shots of vodka, and two glasses of wine for men, and the amounts for women should be approximately half of these.

The liver is an organ that stores glycogen reserves, but alcohol is metabolized in the liver. With a higher consumption of ethanol, glycogen is depleted and alcohol degraded, thus leading to the risk of hypoglycemia. The consumption of alcoholic drinks initially raises blood glucose levels and subsequently, with increased consumption, will lead to hypoglycemia [6]. In clinical practice, it is recommended that alcohol be consumed after eating in order to avoid precipitating the onset of hypoglycemia. Assessing blood sugar levels before and after ingesting alcohol

will indicate the proper amount of insulin. If blood glucose is below 70 mg/dL, alcohol should not be ingested.

### How Is the Amount of Carbohydrates in a Meal to be Assessed?

This assessment may be made by weighing food, but this is a more cumbersome way to do so. Using tables of domestic measures and consulting a manual that counts carbohydrates, in which such measures are used and the amounts of carbohydrates and calories are given in alphabetical order [12], are recommended. Manuals of this kind are already available in paperback. An iPhone app such as Diamigo is already available on the Brazilian market and is a carbohydrate counting program. It is important to note that support and feedback from a professional nutritionist who is a specialist in this field is of great importance in the process of learning and controlling desirable glycemic targets, but is not a substitute for the nutritionist–patient relationship [16, 17]. The basics of carbohydrate counting are shown in Table 39.2.

**Table 39.2** Counting carbohydrates

Group	Example/portions	Amount of carbohydrate
Bread	½ morning roll/1 slice of sliced bread/3 tablespoons of rice/3 water and salt biscuits/½ cup of spaghetti	15 g
Milk	1 240 ml cup of milk/1 cup of yoghurt	12 g
Fruit	1 medium-sized apple/1 medium-sized pear/3 slices of mango/1 small banana	15 g
Vegetables	1 teacup of raw vegetables/½ teacup of cooked vegetables	5 g
Meat	1 small steak/3 soupspoons of minced beef/2 chicken drumsticks	15 g
Fat	1 teaspoon of margarine	0 g

1 steak (medium) = 90 g  
 • Reasoning: 90 g meat = 25 g protein  
 Given that 60 % is converted into glucose,  $25 \times 0.6 = 15$  g carbohydrate

## Effects of Food on the Blood Sugar Level

Carbohydrates raise the blood sugar level by 100 %, proteins by 60 %, and fats by 10 % on average. Carbohydrates raise glucose linearly, i.e., the more the carbohydrates are consumed, the more the glucose level rises. Protein increases the blood glucose level on account of the glyco-genetic amino acids, which play a part in gluco-nogenesis, and fat, because it is ingested more slowly, and maintains glucose levels higher for longer, but does not alter the glucose level as the other macronutrients do.

Some diabetics already use two doses of insulin, one immediately after the meal and the other 2 h later to correct the effect produced by high-fat foods such as pizza, Brazilian beef, and pork stew. The glycemic load of a food is affected by the content of fats, fibers, proteins, coction, and also factors inherent in the individual [6]. As regards fibers, it is recommended that if a food has more than 5 g of fiber, this should be subtracted from the total carbohydrate content of the meal, since fiber decreases the glycemic response [12].

One of the priority aspects of carbohydrate counting is to understand the size of the portion of food, because what will determine the amount of insulin is the amount of carbohydrates in the meal [17]. In performing the carbohydrate count it is important to (1) identify the amount of carbohydrates per meal per day; (2) match the portions of carbohydrates to the meal; and (3) practice the size by measuring or weighing or using as a reference the replicas of food used by nutritionists [12].

When the treatment of diabetes uses oral hypoglycemic agents or the conventional scheme for using insulin, the ingestion of the same amounts of carbohydrates is necessary, since the quantity of the medication is fixed. For patients who use the intensive scheme, it is not appropriate initially to modify the amount of carbohydrates in order that the optimal dose of insulin may be found. Subsequently, however, when one has acquired a better knowledge of the appropriate amount of insulin for the meal in question,

there is greater freedom with regard to varying the amount of carbohydrates per meal [17]. In snacks, since the recommended carbohydrate content is, on average, 15–30 g, no dose of insulin is required because the amount of carbohydrates is not significant.

Another aspect that should be mentioned to the patient is that if he/she still feels hungry, it is better to eat more in main meals. Leguminous food plants such as beans, peas, lentils, and chickpeas should be included in the diabetic diet because they present low glycemic responses, obviously without adding fatty meats to the legumes, since these foods modify the glycemic response of the meal, owing to the higher amount of soluble fibers [6].

Oleaginous foods such as cashew nuts and Brazil nuts, as long as they are eaten in moderation, can and should be part of the menu for diabetic patients, as well as for pregnant women with gestational diabetes, because they are rich in omega 3 from the vegetable kingdom, monounsaturated fat, and selenium, having 70 % good-quality fat and a low glycemic response, but the consumption of 12 cashew nuts or 4 Brazil nuts already represents 90 cal. They are a good option for snacks or for adding to salads.

Patients who enjoy Japanese food should consider that for every sushi, there is a corresponding one tablespoonful of rice and that sugar is used as part of the mixture, besides being an ingredient of cucumber sunomono. The blood glucose level should therefore be measured before the meal, the average consumption and corresponding dose of insulin checked, and the capillary glucose verified 2 h later.

Since Italian cuisine uses a large amount of cheese, there is a need to split the dose of insulin because of the delayed effect of the action of the fat on blood glucose. Currently counting is done because it affords diabetic patients greater freedom [15, 16]. However, the individual needs to be aware that insulin is a lipogenic hormone and thus the consumption of carbohydrates should be proportional to that of insulin [17]. In other words, if the patient needs to lose weight, there is a need for fewer carbohydrates in the meal so that a lesser amount of insulin is made available.



The IDF considers that there is a considerable volume of scientific evidence that diets with a low glycemic load are beneficial for controlling postprandial glucose [3]. The glycemic load represents the glycemic index per edible portion of food [6]. In other words, it is an objective way of measuring the extent to which food modifies the postprandial response. The percentage of protein should be less than 20 % [15], since in clinical practice we observe a tendency for diabetic patients to consume protein in larger quantities, which, according to the literature, seems to raise the glomerular filtration rate, which is undesirable in the diabetic population.

Sometimes patients may have doubts as to whether a particular food raises blood glucose levels. In this situation, after 4 h without eating food, from a metabolic viewpoint, it is as if there had been a return to fasting. This provides an opportunity for the individual to measure his/her preprandial blood sugar level and, 2 h later, to observe the impact that the test food has on the blood glucose level.

Some foods, because they contain small amounts of carbohydrate (less than 5 g) or few calories, need not be taken into consideration in the food schedule of the diabetic [10]. These foods are listed in Table 39.3. Although it is known that low sucrose does not seem to hamper glycemic control and that what is important is the quantity and frequency with which food is included in the diet plan, the frequent consumption of sucrose is not recommended, because foods rich in sucrose are also rich in saturated fats, in addition to raising the blood glucose level more quickly [12].

In northeastern Brazil, due to sugarcane cultivation, the consumption of sugar should be discouraged because an expressive quantity is already consumed in this region.

Foods such as white bread, couscous, and potatoes should be used with due care in the diabetic's diet because they produce high blood glucose levels [6], but should never be prohibited as diabetes is a chronic disease. The same is true for the following: banana, mango, jackfruit, orange juice, plums, and raisins. These should be avoided, particularly in periods of decompensation, and consumed preferably before undertaking any

**Table 39.3** List of foods with less than 5 g of carbohydrates

Food	Portion limit
Sweetener	Use at most 3 drops at one time
Diet sweet	1 small tin or 10 units per day
Coffee or tea with sweetener	Use at most 5 drops of sweetener per cup
Diet chewing gum	10 units per day
Diet gelatine	1 box (approximately 5 cups) per day
Diet jelly	1 full (dessert) spoon at breakfast and another one at supper
Ice cream zero% fat	1 small dish midmorning and another as an afternoon snack
Ketchup or mustard	1 full (soup) spoon per day
Diet, light, or zero soft drink	2 cans or 3 small cups (200 ml) per day

**Table 39.4** Label on foods

<i>No calories:</i> Products which have < 5 kcal/portion
<i>Low calorie:</i> Products which have $\leq 40$ kcal/portion
<i>Low cholesterol:</i> The portion contains $\leq 20$ mg cholesterol and $\leq 2$ g saturated fat
<i>Low fat content:</i> The food has $\leq 3$ g fat/portion
<i>No fat:</i> The food has <0.5 g fat/portion
<i>Low content of saturated fat:</i> Other food has $\leq 1$ g saturated fat/portion
<i>Low content of sodium:</i> Foods which contain $\leq 140$ mg sodium/portion
<i>Very low sodium content:</i> Foods which contain $\leq 35$ mg sodium/portion

physical exercise or when blood sugar levels are lower than usual.

Labels need to be read (Tables 39.3 and 39.4) [10]. When eating outside the home, a self-service establishment is preferable as consumption can more easily be kept to what has been recommended, while *à la carte* restaurants should be preferred to barbecue houses, which encourage consumption in excess. In cafeterias, sandwiches with fatty cheese should be avoided. Wholemeal bread is to be preferred and fried food, sauces with mayonnaise, or sour cream avoided, while bread and potatoes should not be eaten during the same meal.

In situations of hypoglycemia the recommended consumption is as follows: one glass of an ordinary soft drink or one glass of orange juice or one soup spoon of sugar and three caramel toffees [6]. Liquid consistency is better because the food is more easily absorbed than solid foods.

Foods such as chocolate should be avoided as their fat content raises blood sugar more slowly. Episodes of hypoglycemia are the result of excessive physical activity, eating smaller amounts of food than necessary, or using more insulin than is appropriate.

The professional nutritionist needs to:

- Assess nutritional status
- Perform dietary anamnesis
- Calculate the diet plan and prioritize the macro- and micronutrients according to the ADA guidelines
- Provide the amount of carbohydrates according to the amount of ultrarapid or regular insulin [12, 17]
- Check the individual's sensitivity factor
- Evaluate the pre- and postprandial blood glucose levels and adjust the doses according to the postprandial responses in conjunction with the diabetologist
- Monitor nutritional status [18], glycemic and lipid profiles, and renal function [4, 5], adjusting the diet when necessary

## Concluding Remarks

Previously food programming was calculated and offered to the individual with diabetes, together with nutritional guidelines. Currently, using the food anamnesis collected, the professional will adapt eating habits as closely as possible to the patient's eating habits, everyday life, individual preferences, and sociocultural profile. The orientation of carbohydrate counting, insulin analogues, and insulin pumps provide greater freedom and a better quality of life for this population. Thus, controlling blood glucose levels in these patients, thereby stimulating their pleasure in eating in a balanced way, is a priority and a major challenge for nutritionists.

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## Diagnosis

### Lipid Profile

The lipid profile is composed of laboratory measurements of TC, TG, HDL-C, and LDL-C. Traditionally, LDL-C is not measured directly in plasma, as calculated by the Friedewald equation [6]  $LDL-C = TC - HDL - TG/5$ .

However, this equation is no longer accurate when TG levels are greater than 200 mg/dL and ceases to be valid when they exceed 400 mg/dL or in the presence of chronic diseases such as cholestatic liver disease, poorly controlled diabetes mellitus (DM) and nephrotic syndrome [7]. In these cases, direct LDL-C can be performed through specific tests with excellent precision and accuracy [8].

Table 40.1 shows the values for the different lipids according to NCEP/ATP [9]. On finding a patient with a changed lipid profile, one must first

determine the cause of this change, which means looking for a secondary cause (Table 40.2) and asking about family history in the search for a genetic cause (primary dyslipidemia).

### LDL-Cholesterol

The increase in cardiovascular risk has been associated not only with elevated levels of TC, but also with an increase in LDL-C [10, 11]. More recent studies have shown that this association is not linear and a steep increase in risk occurs when the levels of LDL-C affect more elevated track levels [12]. In addition, several randomized studies have shown that the control of total cholesterol and LDL-C levels is associated with a decreased risk of cardiovascular events in different groups of patients [13, 14].

Even in the presence of normal levels of LDL-C, the individual may experience an increase in the small, dense LDL particles. These particles react more easily in the arterial wall and are more susceptible to oxidation. They are therefore associated with an increased risk of cardiovascular events and may be present in 50 % of men with CAD. Their presence is often related to low levels of HDL-C and hypertriglyceridemia, as well as metabolic syndrome (MS) and DM [15].

### HDL-Cholesterol

Low levels of HDL-C are related to increased cardiovascular risk, as evidenced by the Framingham Heart Study, which showed an increased risk of acute myocardial infarction of about 25 % for every 5 mg/dL decrease in

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**Table 40.1** ATP III classification of total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride

Total cholesterol (mg/dL)	
< 200	Desirable
200-239	Boderline high
≥240	High
HDL cholesterol (mg/dL)	
<40	Low
>60	High
LDL cholesterol (mg/dL)	
<100	Optimal
100–129	Near optimal
130–159	Boderline high
160–189	High
≥190	Very high
Triglyceride (mg/dL)	
<150	Normal
150–199	Boderline high
200–499	High
≥500	Very high

**Table 40.2** Secondary causes of dyslipidemia

↑ Total cholesterol and LDL-cholesterol	↑ Triglyceride
Hypothyroidism	Diabetes mellitus, hypothyroidism
Nephrosis	Chronic renal failure
Systemic lupus erythematosus	Obesity
Multiple myeloma	Excessive alcohol intake
Anabolic steroid treatment	Corticosteroid, protease inhibitors
Cholostatic diseases	Thiazide diuretics, β-adrenergic blocking
Protease inhibitors	Orally administered estrogens

HDL-C [16]. Studies such as LIPID, CARE, and TNT have reported that low levels of HDL-C are more powerful predictors of cardiovascular events in patients with LDL-C levels less than 125 than in those with levels higher than 125 mg/dL [17, 18].

On the other hand, HDL-C levels >60 mg/dL have been considered a negative risk factor for CAD, so one risk factor can be subtracted from a patient's overall risk profile [15]. In both sexes HDL-C levels below 40 mg/dL are an independent risk factor for CVD. However, women tend to have higher levels of HDL-C than men, so values >50 mg/dL are considered ideal for females [15].

## Triglycerides

Hypertriglyceridemia has also been linked to an increased risk of cardiovascular events, as well as an increased mortality in patients with established CAD [19, 20]. This relationship may be due to the direct effect of hypertriglyceridemia as an association of this condition with some other factors that predispose to atherosclerosis, such as low HDL-C, increased coagulation, insulin resistance, and the presence of small, dense LDL-C particles [21]. Some studies, such as SCRIP, which described the presence of small, dense particles in 90 % of individuals with triglyceride levels above 160 mg/dL [22], have found an inverse relationship between triglyceride levels and LDL-C diameter.

An additional test that can be performed in an individual with elevated fasting TG is the determination of postprandial triglyceridemia. Some evidence indicates that the TG-rich lipoproteins produced in the postprandial period are atherogenic and that levels of postprandial TG > 150 mg/dL are an independent risk factor for CAD. Better standardization of this cutoff point is, however, still required [23–26].

## Non-HDL Cholesterol

In patients with hypertriglyceridemia, in addition to increased LDL, there is an increase in IDL and VLDL, all atherogenic lipoproteins. Thus, the non-HDL cholesterol estimates the total circulating atherogenic lipoproteins better than LDL-C and also appears to better estimate cardiovascular risk [27, 28], especially in patients with TG between 200 and 500 mg/dL, diabetes, and established cardiovascular disease (CVD) [29, 30]. Non-HDL cholesterol should be determined by calculating the difference between the total cholesterol and HDL-C in patients with triglyceride levels greater than 200 mg/dL. The non-HDL cholesterol target is 30 mg/dL higher than established LDL-C risk levels [9].

## Additional Tests

### Lipoprotein (a)

Lipoprotein (a) corresponds to an LDL-C particle which is found connected to a specific apolipoprotein: apo (a). Serum levels are genetically

determined and the apolipoprotein (a) molecule has an important homology to plasminogen, so there is a competitive effect on the latter. This leads to a prothrombotic effect, thus contributing to atherosclerotic vascular injury [31]. Different studies have shown increased levels of lipoprotein (a) to be an important independent risk factor for coronary artery disease and cerebrovascular disease, especially in Caucasian patients [32, 33].

However, the lack of standardization in the measurement of this lipoprotein limits its use, so its evaluation is not routinely recommended. Nonetheless, its determination could be useful in white patients with CAD and in subjects with a family history of CAD of unknown origin [15].

### C-Reactive Protein

C-reactive protein (CRP) is a highly sensitive marker of chronic inflammatory conditions such as atherosclerosis, and its elevation has been associated with increased cardiovascular risk. Its levels can be divided into <1 mg/L (low risk), 1–3 mg/L (intermediate risk), and > 3 mg/L (high risk) [34]. However, the JUPITER study recently suggested a simpler stratification: CRP <2.0 vs.  $\geq$ 2.0 [35].

Although some studies have suggested that CRP could be a better predictor of cardiovascular risk better than LDL-C [36], larger, more recent studies have shown that the dosage adds little to predictions based on the traditional risk factors [34]. In relation to therapeutic drug monitoring, CRP levels seem to play a more important role since, as demonstrated by a recent study, the reduction in risk of coronary events appears to be greater not only when the LDL-C drops below 70 mg/dL but also when CRP has decreased levels in response to treatment (less than 2 mg/L) [37].

The dosage of CRP, however, should not be performed routinely, but may be useful in estimates of intermediate risk or in evaluating residual risk in patients with LDL-C <130 mg/dL [15].

### Homocysteine

Elevated levels of homocysteine (>15  $\mu$ mol/L) have also been associated with increased cardiovascular risk [38, 39]. However, reduction in its levels with the use of folic acid, vitamin B6, and vitamin B12 showed no risk reduction [40]. Routine screening is

therefore not recommended, but in patients stratified as intermediate risk by the Framingham Risk Score (FRS) (see below), its determination can be useful in modifying the rating for high risk [15].

### Apolipoproteins

Serum levels of apolipoprotein B (apo B) reflect the levels of small, dense LDL particles, recognized as atherogenic. Some studies have suggested that the elevation of apoB is equivalent or even superior to LDL-C and non-HDL-cholesterol in predicting cardiovascular risk, even in patients with insulin resistance and DM2 [41–43]. The optimal level of apoB recommended in patients at risk of CAD is below than 90 mg/dL [15].

Perhaps even more useful is the assessment of apoB/apolipoprotein AI (apoA-I), as this ratio has been a stronger risk predictor than the LDL-C/HDL-C ratio [44]. The dosage of apoB and apoA-I is indicated in patients with TG > 150 mg/dL and HDL-C below 40 mg/dL to assess residual risk, even in those with LDL-C within the target range, including patients with CAD and DM2 [15].

### Carotid Intima-Media Thickness and Coronary Calcium Score

The measurement of carotid intima-media thickness (IMT) and the coronary calcium score (CCS) are noninvasive imaging tests and have emerged, in recent years, as markers for CAD.

The CCS is an estimate of the amount of coronary plaques in an individual [45]. A CCS of zero reflects a low likelihood of coronary disease and the patient is classified as low risk, with an annual event rate of only 0.11 % in the asymptomatic individual [46]. This appears to be true even in diabetic patients, as it has already been shown that in these cases a CCS of zero indicates survival similar to nondiabetic patients also with a CCS of zero, so in these cases, lipid-lowering therapy would not need to be as aggressive or even necessary [47]. However, studies comparing the CCS with the carotid IMT have suggested that the latter, when increased, has proved a better predictor of CAD [48].

These tests, in any case, are not yet recommended in all individuals with dyslipidemia and

**Table 40.3** Coronary artery disease risk categories and low-density lipoprotein treatment goals [15]

Risk category	Risk factors/10-year risk <sup>a</sup>	LDL-C treatment goal
Very high risk	Established or recent hospitalization for coronary, carotid, and peripheral vascular disease or diabetes plus 1 or more additional risk factor(s)	<70 mg/dL
High risk	≥2 risk factors and 10-year risk >20 % or CHD risk equivalents <sup>b</sup> , including diabetes with no other risk factors	<100 mg/dL
Moderately high risk	≥2 risk factors and 10-year risk 10–20 %	<130 mg/dL
Moderate risk	≥2 risk factors and 10-year risk <10 %	<130 mg/dL
Low risk	≤1 factor risk	<160 mg/dL

<sup>a</sup>Framingham risk scoring is applied to determine 10-year risk

<sup>b</sup>Diabetes and clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease)

their usefulness would probably be greater in those patients initially classified as intermediate risk, in whom they could provide a better explanation of the need for therapy and lipid goals.

### In Whom Should Serum Lipids Be Measured?

The lipid profile should be carried out in every adult from the age of 20. In patients without risk factors and an appropriate lipid profile, the test can be repeated every 5 years [9]. From the age of 45 years in men and 55 years in women, this frequency should be increased to one to two times a year, considering the high prevalence (21–49 %) of dyslipidemia in this age group as evidenced by some studies [49, 50]. From 70 years of age, annual screening is recommended [16]. In patients with multiple risk factors for CVD, the lipid profile should be repeated more frequently regardless of age group [15].

Screening for dyslipidemia should also be performed in all patients with established coronary artery disease (CAD), diabetes, hypertension, obesity, and family history of primary dyslipidemia [9].

### Cardiovascular Risk Assessment

The diagnostic approach to dyslipidemia involves not only the diagnosis but also the assessment of cardiovascular risk to which the

individual is exposed. This risk stratification is essential to initiate the most appropriate treatment for the patient. After all, not all patients with abnormal lipid levels are candidates for drug therapy, and both the indication for and the aggressiveness of therapy to be instituted should be based on the individual risk of developing CVD. The risk that an individual has of a coronary event in 10 years (death or MI) can be classified as high (greater than 20 %), intermediate (between 10 and 20 %), and low (less than 10 %) [51].

In an attempt to establish goals for lipid control-based risk, the National Cholesterol Education Program (NCEP) has, since 1988, been developing guidelines, the main objective of which is the reduction in LDL-C. Its latest version was published in 2001 [9], being updated in 2004 [52] through the Adult Treatment Panel III (ATPIII), and classifies coronary risk according to the presence of risk factors and estimates of the FRS: low, moderate, moderately high, and high risk. More recently, patients with recent coronary, carotid, or peripheral vascular disease or with type 2 DM associated with at least one risk factor, in which the LDL-C treatment goal is less than 70 mg/dL [52], are considered to be at very high risk (risk > 40 % in 10 years). Based on this, the most recent guideline published by the American Association of Clinical Endocrinologists stratifies the subject into five different categories of risk [15] (Table 40.3).

**Table 40.4** Major coronary artery disease risk factors

Advancing age
High total serum cholesterol level
High non-HDL-C
High LDL-C
Low HDL-C
Diabetes mellitus
Hypertension
Cigarette smoking
Family history of coronary artery disease <sup>a</sup>

<sup>a</sup>Definite myocardial infarction or sudden death before age 55 years in father or other male first-degree relative or before age 65 years in mother or other female first-degree relative

The first step in estimating risk is to identify the presence of current manifestations of atherosclerotic disease (CAD, cerebrovascula, and peripheral vascular disease). Likewise, attention must be paid to the occurrence of the atherosclerotic disease equivalents such as diabetes type 1 or 2 and abdominal aortic aneurysm, which would put the individual in the category of high risk at least [51]. Subsequently, the presence of major risk factors for atherosclerotic disease (Table 40.4) and ERF should be evaluated [15]. The ERF is most useful in cases initially classified as intermediate risk.

The Framingham study, conducted in the USA, provided sufficient epidemiological evidence to permit risk evaluation of CAD in 10 years in an individual, using scores and cardiovascular risk tables. The FRS considers blood pressure, sex, age, smoking status, and TC and HDL-C levels [2]. If the risk is classified as intermediate, there is a need to consider other factors associated with cardiovascular risk to minimize the possibility of under- or overestimating the risk.

Thus the classical risk factors do not appear sufficient to predict all risk, and in this context the role of the emerging risk factors (C-reactive protein, lipoprotein (a), apoB/apoAI ratio, microalbuminuria, homocysteine, left ventricular hypertrophy, the thickness of the carotid artery intima-media complex (IMT), CCS) has been gaining strength.

## Treatment

### Treatment Goals

The reduction in LDL-C levels, especially in individuals at risk of CVD, remains the main therapeutic target in dyslipidemia. Table 40.4 shows the goals for each risk category and drug treatment associated with lifestyle modification (LSM) in patients at high or very high risk should be initiated immediately, having statins as first-choice drugs. Even if the initial target is not reached, the reduction of at least 30–40 % in the initial LDL-C levels has shown a decrease in cardiovascular risk [9]. However, a single LDL-C target, in general, is not sufficient to reduce all cardiovascular risk [15].

The goal for TG is < 150 mg/dL. However, the exact level at which TG starts to confer risk is unknown. Endocrine Society Guidelines suggested a new TG classification: mild hypertriglyceridemia (150–199 mg/dL); moderate hypertriglyceridemia (200–999 mg/dL); severe (1,000–1,999 mg/dL); and very severe ( $\geq 2,000$  mg/dL) hypertriglyceridemia [53]. Lifestyle changes (LSC) should be started in the presence of hypertriglyceridemia, and drug therapy in cases in which LSC failed. Only in those individuals with TG > 1,000 mg/dL, drug therapy should be started immediately, preferably a fibrate, to reduce the risk of pancreatitis [53].

For HDL-C, in the presence of associated hypertriglyceridemia or other risk factors, a target at least >40 mg/dL should be pursued. The major question occurs in individuals with isolated lowering of HDL-C in the absence of CVD and/or risk factors due to the absence of clinical trials supporting the benefit of increasing this lipid in this group of patients [15]. However, once it has been decided to raise their HDL-C levels, regular physical activity should be instituted and smoking cessation should also be encouraged, as these measures are known to be effective in increasing HDL-C. If a drug is required, nicotinic acid remains the most effective option.

## Lifestyle Change

All patients with dyslipidemia should initiate LSC, based on diet reorientation (low in saturated fat and high in fiber), regular physical activity, and smoking cessation. This therapeutic approach corresponds to the first option in patients at low risk, in which pharmacological treatment should only be initiated 6 months after an attempt to normalize lipemia with LSC, and in those at intermediate risk, in whom the start of lipid-lowering medication should be considered only 3 months later [9].

The type of fat intake is fundamental to the management of dyslipidemia. The saturated fat intake should be limited (<7 % of total calories), and trans fats should also be avoided, since they are associated with elevated LDL-C, decreased HDL-C, and increased cardiovascular risk. Unsaturated fatty acids should make up 10–20 % of caloric intake. Polyunsaturated fatty acids are represented by omega 3 (found in vegetable oils and cold-water fish), the benefits associated with CVD; omega 6 (found in soybean, corn, and sunflower oil), associated with reduction in LDL-C; and TG, although they can also decrease HDL-C. Monounsaturated fatty acids reduce LDL-C, but with no effect on the HDL-C [9].

Considering the positive effect of omega 3 on the lipid profile and cardiovascular risk, its supplementation (at least 1 g of fish oil a day) has been recommended for patients with CVD [15].

## Statins

Statins represent the drugs of choice in hypercholesterolemia treatment. They act by inhibiting HMG-CoA reductase, an enzyme involved in the synthesis of endogenous cholesterol. Since the intracellular levels of cholesterol decrease with the use of the drug, there is an increase in LDL-C receptors in cell membranes, enhancing LDL-C clearance [54].

The decrease in LDL-C serum levels can range from 25 to 55 % depending on the drug used. There may also be a fall in triglyceride levels of 15–25 % and an increase in HDL-C of around 2–10 % [55].

Simvastatin (dose of 20–80 mg per day) and pravastatin (dose of 20–40 mg a day) must be taken at night. However, atorvastatin (dose of 10–80 mg per day) and rosuvastatin (dose of 10–40 mg per day), more potent in reducing LDL-C, have a longer half-life and can therefore be administered at any time of the day. Rosuvastatin is the most effective drug for raising HDL-C levels [55].

On the whole, it is not recommended to exceed the dose of 40 mg of simvastatin and of 20 mg of atorvastatin and rosuvastatin, because larger doses will contribute little to the decrease in LDL-C and there is an increased risk of side effects. Thus, in the absence of response, the most sensible thing to do is to introduce another class of drug.

In general, statins are well tolerated, although the following may occur: hepatotoxicity in 1.4 % of cases (a >3-fold increase in transaminases indicates a dosage reduction or discontinuation of the drug), and myalgia and CPK elevation to 15.4 and 0.9 % of cases, respectively (in cases of a >10-fold rise in CPK or persistence of muscle symptoms, the drug should be discontinued). Rhabdomyolysis is rare, occurring in 0.2 % of individuals, and its risk increases in cases of association of drugs with fibrates (except fenofibrate). Among the contraindications to statin therapy, the following may be mentioned: pregnancy, breastfeeding, and acute liver diseases (in cases of renal failure and chronic liver disease, the drug can be used) [56].

Recent clinical trials suggested that the statins may increase the incidence of diabetes. A meta-analysis of 13 randomized statin trials of over 91,000 patients suggested that these drugs compared with placebo leads to a 9 % increased relative risk for the development of diabetes [57]. However, the benefit of cardiovascular risk reduction by statin therapy seems to exceed the risk of diabetes. A risk-benefit analysis showed that the risk of diabetes was increased, but the statins were favorable in high-risk and secondary prevention populations [58]. A recent analysis from the JUPITER (a primary prevention trial) evaluated 17,603 subjects without previous CVD or diabetes and showed that, in subjects with one



or more diabetes risk factors, the statin therapy was associated with a 39 % reduction in the primary endpoint (myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularization, or cardiovascular death) and a 28 % increase in diabetes (a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed) [59].

The major advantage of statins is their positive effect on cardiovascular disease, constituting a class of drug with strong evidence of reducing overall mortality when used in both primary and secondary prevention.

### **Benefits in Secondary Prevention**

Several studies have reported the benefits of statin therapy in patients with proven CAD, regardless of the presence of dyslipidemia.

The 4S study compared simvastatin (up to a maximum dose of 40 mg) with placebo and, in addition to reporting a decrease in coronary events and CAD mortality, it was the first study to show a decrease in overall mortality [13]. CARE, in turn, compared placebo with pravastatin, also showing a reduction in the incidence of coronary events and deaths from CAD [60]. HPS (UK Heart Protection Study), comparing simvastatin 40 mg with placebo, showed a reduction of about one-third in the risk of myocardial infarction (MI), stroke, and myocardial revascularization, in addition to its beneficial effect on overall mortality and CAD, irrespective of baseline cholesterol (33 % had LDL-C lower than 116 mg/dL). The benefit in patients with low LDL-C levels reflects a possible additional effect of statins in addition to that related to the reduction in cholesterol levels [61].

In relation to the statin dose, there is no justification for the use of aggressive therapy in stable patients. CARDS, for instance, demonstrated that the use of atorvastatin at a dose of 10 mg, in type 2 diabetics, was able to reduce the risk of cardiovascular events by 35 % [62]. Also, even though TNT has shown that 80 mg of atorvastatin has led to an additional reduction in events when compared to a 10-mg dose, there was a higher incidence of adverse effects with the higher dose [18]. Furthermore, a recent meta-

analysis of data from more than 30,000 patients without DM showed that intensive therapy was associated with an increased occurrence of new cases of DM [63].

Aggressive treatment, however, has proven its benefits in patients with acute coronary syndrome (ACS). In this case, the drug should be started even prior to discharge from the hospital stay and in high doses, as shown by studies PROVE-IT and MIRACL, demonstrating the advantage of an 80-mg dose of atorvastatin compared to a less aggressive therapy (pravastatin at a dose of 40 mg) [64, 65]. The absence of similar results using an 80-mg dose of simvastatin in ACS, shown by the A to Z study, suggested that in patients with high levels of inflammation, statins are important because of their pleiotropic effects [66]. Thus an aggressive treatment is justified only for ACS cases and atorvastatin at a dose of 80 mg should be the drug of choice in this situation.

### **Beneficial Effects on Atheromatous Plaque**

Both REVERSAL and ASTEROID have studied stable coronary patients accompanied with intracoronary ultrasound and showed that the use of 80 mg of atorvastatin led to plaque stabilization (REVERSAL) and that rosuvastatin induced the regression of atheroma (ASTEROID) [67, 68]. METEOR, in turn, studied patients at low risk (primary prevention), showing that there was progression of carotid IMT in individuals who used the placebo compared with those on rosuvastatin 40 mg for 2 years [69].

A recent study compared rosuvastatin and atorvastatin at maximum doses and demonstrated a similar effect on atheroma volume reduction, despite the greater effects of rosuvastatin on LDL-C and HDL-C [70].

### **Benefits of Primary Prevention**

WOSCOPS was a primary prevention study in middle-aged men which showed a reduction in coronary events and mortality in this group of patients with the use of pravastatin 40 mg/day [71]. The same was observed for the AFCAPS/TexCAPS (with lovastatin) and ASCOT-LLA

(with atorvastatin 10 mg), both with the added advantage of having also evaluated women and having included patients with cholesterol levels closer to “normal” [14, 72]. More recently, JUPITER compared the use of rosuvastatin with placebo in patients with LDL-C <130 mg/dL, but with CRP  $\geq$ 2.0 mg/L, being discontinued owing to the evident reduction in cardiovascular morbidity and mortality in the statin group [35].

Although there is evidence of benefits of primary prevention treatment, not all patients should be treated, so the cost–benefit should be considered (4S estimated the cost per life saved per year for secondary prevention of about US\$ 7,500, whereas WOSCOPS estimated a cost of US\$ 27,000 for primary prevention) [13, 71]. Treatment should therefore be reserved for those patients with a higher CAD risk, considering the LDL-C levels and associated risk factors.

## Fibrates

Fibrates are the drugs of choice in hypertriglyceridemia treatment and reduce TG by 20–35 %, but they also have an effect on HDL-C (elevation of 6–18 %) and on LDL-C (variable effect, reducing or even increasing its levels). They act via activation of peroxisome proliferator-activated receptor alpha (PPAR- $\alpha$ ), leading to the activation of lipoprotein lipase (LPL) (responsible for the hydrolysis and removal of plasma triglycerides); reduced VLDL synthesis in the liver; and increased synthesis of apoAI, contributing an increase in HDL-C [15].

Among the main fibrates, the following deserve special mention: gemfibrozil (600–1,200 mg/day), fenofibrate (200 mg/day in its micronized form), and ciprofibrate (100 mg/day). They can cause fatigue, gallstones, gastrointestinal disturbances, rash, headache, and, more rarely, elevated transaminases and CPK. Rhabdomyolysis has been described when statins are associated with gemfibrozil, which therefore should not be used in this type of combination therapy. Fibrates should be avoided in cases of renal failure [73].

Although there is a decrease in lipid levels with the use of fibrates, they have not been shown, in the long term, to produce the same clinical results as statins. Some studies, however, such as the Helsinki Heart Study and BIP [74, 75], have demonstrated a reduction in coronary events. The FIELD study involving 9,795 subjects with DM2 showed that micronized fenofibrate decreased coronary events, but increased coronary mortality in all cases. However, the results were not significant [76].

## Niacin

Niacin can be used instead of fibrates and statins (or in association with them) in the treatment of hypercholesterolemia, hypertriglyceridemia, or mixed hyperlipidemia, since it reduces the hepatic synthesis of VLDL and, consequently, its LDL-C metabolite. But the action that makes it unique among oral lipid-lowering drugs is its inhibitory effect on the transport of cholesterol from HDL-C to VLDL and on the clearance of HDL-c, thereby increasing the plasma levels of this lipoprotein [77].

Niacin is, therefore, the most effective drug for treating patients with low levels of HDL-C without other lipid abnormalities, and can increase HDL-C by 30 %. To exert its effect on HDL-C, in general, doses of 1–1.5 g/day are necessary. Higher doses (3 g/day) are more effective on LDL-C and triglycerides as well as on lipoprotein (a), which can be reduced by 35 % [78].

There are three types of drug preparation, according to the speed of its release: fast (often causes flushing), intermediate (causes less flushing), and slow (the main limitation of which is hepatotoxicity). Of these three, the second is the option of choice and should be initiated at a dose of 500 mg, with a gradual increase (every month) to 1–2 g/day as a single dose taken immediately after dinner.

The biggest question now about this drug is whether there would be some benefit from its combination with statins in the prevention of cardiovascular events. Studies evaluating the use of statins plus niacin in CAD patients showed that

this association decreased mortality and cardiovascular events, suggesting an additional protection when therapy for an increase in HDL-C is instituted [79]. The ARBITER2 study, in turn, showed a tendency of reduction in carotid IMT progression with the use of niacin in coronary patients already on statins, suggesting a beneficial effect of the drug on the anatomical progression of atherosclerosis [80].

However, the more recent AIM-HIGHT study failed to show any additional benefits of adding niacin to statin therapy in patients with a mean LDL-C of 71 mg/dL, and suggested a higher occurrence of stroke in individuals treated with niacin [81]. This study, therefore, increased doubts about the advantage of the combination of statin and niacin, so one must await the results of HPS2-THRIVE, currently in progress, for clarification of this issue.

Among the side effects of drugs, the main one is flushing, mediated by the action of prostaglandin D and often responsible for the discontinuation of therapy. This effect can be prevented with the use of aspirin 325 mg 30 min before drug intake. More recently laropiprant, a prostaglandin receptor antagonist, has been used in combination with niacin, significantly reducing the incidence of flushing, as well as its intensity, without changing the lipid effect [82].

A negative effect of the drug on glucose metabolism with increased insulin resistance and elevated blood glucose has also been demonstrated. However, these changes have been shown to be transient and can be effectively controlled with adjustments to the treatment regime with oral antidiabetic agents or insulin in individuals with DM2 [15, 83].

## Ezetimibe

Ezetimibe is used at a dose of 10 mg/day in the treatment of hypercholesterolemia, reducing intestinal cholesterol absorption by inhibiting the cholesterol transport protein present in the brush border of the enterocyte without interfering with the absorption of fat-soluble vitamins and triglycerides [15].

Although its use alone can reduce LDL-C by about 17 %, its main therapeutic use is in combination with statins in an attempt to avoid the need to increase the dose of the latter in unresponsive cases [84]. Ezetimibe can produce a further 14 % reduction in LDL-C levels when added to the isolated use of statins and has the advantage of being well tolerated [85]. Additional benefits have also been demonstrated by its association with atorvastatin and rosuvastatin [15].

However, there is still no conclusive data showing the benefits of this drug in reducing cardiovascular events. ENHANCE, involving 720 patients with familial heterozygous hypercholesterolemia, showed no significant difference in the progression of carotid IMT between the group treated with statin alone and those associated with ezetimibe, despite the more significant reduction in LDL-C in the second group [86]. On the other hand, the SHARP study showed a reduced incidence of cardiovascular events in subjects with chronic renal failure using simvastatin 20 mg/day plus ezetimibe 10 mg/day [87]. In addition, preliminary data from SEAS have shown a 20 % reduction in ischemic events by 20 % in the group using simvastatin 40 mg/day plus ezetimibe 10 mg/day when compared to the placebo group [88]. More conclusive results are expected with the completion of IMPROVE-IT in 2013.

## Bile Acid Sequestrants

Colestipol, colestevlam, and cholestyramine act by inhibiting the absorption of bile salts, which, as a result, reduces cholesterol absorption. They are therefore options in the treatment of hypercholesterolemia, particularly in combination with statins, and can decrease LDL-C by 15–25 %. They can also raise HDL-C slightly (4–8 %), but should be avoided in hypertriglyceridemia, since they may increase TG levels [15]. One advantage of the use of colestevlam is the reduction of blood glucose levels and it can serve as an adjuvant therapy for DM2 [89].

Its main drawback is the impaired tolerance resulting from its gastrointestinal effects (nausea, meteorism, constipation), leading eventually to

high rates of noncompliance. Colesevelam, however, seems to be better tolerated [15].

## Combination Therapy

In many situations, the isolated use of only a single lipid-lowering agent is not sufficient to achieve lipid targets, and it is preferable to combine two different classes of drug rather than increase the dose of the medication in use. After all, in the treatment of hypercholesterolemia, for example, an increase in dose can only further reduce by 6 % in the amount of LDL-C, in addition to which it considerably increased the risk of side effects such as increased liver transaminases and muscle injury.

Combination therapy is therefore usually recommended when (1) monotherapy fails to reduce cholesterol levels to the desired target; (2) increasing the dose of medication in use is accompanied by adverse events; or (3) the patient has a mixed dyslipidemia (elevated LDL-C and TG with HDL-C reduction).

In the first case, three types of combination can be considered: statin + ezetimibe, especially after the positive results presented by SHARP, although this combination needs to be better evaluated in future studies [84]; statin + bile acid sequestrants; and statin + niacin, a combination whose cardiovascular benefit remains inconclusive [15].

In the presence of side effects with the increase of statin doses, the best matches would be combinations with ezetimibe or bile acid sequestrant. In cases of mixed hyperlipidemia, the combination with fibrates, avoiding gemfibrozil, or with niacin is the best option [15].

## Future therapies

New pharmacological interventions may help, in a near future, to decrease the residual cardiovascular risk which is still significant in patients on statin therapy [90]. Lomitapide, a microsomal triglyceride transfer protein inhibitor which

blocks the secretion of APO-B by the liver, and mipomersen, an antisense nucleotide which leads to Apo B RNA degradation, are approved for the treatment of homozygous familial hypercholesterolemia (HoFH). Their effects on LDL-C reduction are from 25–60%. The frequent finding of fat liver disease with these drugs limits their use at this point. Another class of drugs that are in phase III trials, targets the proprotein convertase subtilisin/kexin type 9 (PCSK9, a protein secreted by the hepatocyte that regulates the surface expression of LDL receptors by targeting them for lysosomal degradation. Two monoclonal antibodies to PCSK9 are in clinical trial development and their LDL-C lowering effects are around 70% in patients on background of statins. Ongoing studies with two CETP (cholesterol esters transfer protein) inhibitors (anacetrapib and evacetrapib) will provide evidence regarding cardiovascular risk reduction when targeting HDL-C. These compounds can raise HDL-C by 80–100% in patients on background of statins.

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## Key Issues to be Discussed

- The prevalence of obesity is growing in the Western world and very little is being offered for its treatment
- Lifestyle modification is often considered the best long-term treatment but its results are generally poor and disappointing
- Lifestyle modification includes a low-calorie diet, with data suggesting equivalence of results with diets of different macronutrient compositions, and aerobic physical activity
- Combining lifestyle modification with pharmacological therapy is a more effective method of treatment, but few long-term drugs are available to date
- The FDA approved two new weight-loss drugs in 2012 after a 13-year hiatus
- Combinations of drugs for the treatment of obesity have many potential advantages but few have been studied to date
- Surgical procedures, particularly bariatric surgery, are safe, effective and are becoming more popular and widespread, but it only applies to a fraction of the obese population

- Bariatric surgery is the only proven treatment of obesity that reduces long-term mortality

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## Lifestyle Modification

It is well known that eating less and exercising more leads to weight loss. It is also recognized that such weight loss is heterogeneous, with some subjects achieving good and sustained weight loss after a diet+exercise program and some subjects achieving minimal weight loss [8]. Even in those individuals with a good initial response, adaptive mechanisms, like increased hunger and lower energy expenditure, will likely lead the individual to regain weight in middle to long term [9]. An exception is intervening physiological conditions like pregnancy and lactation or voluntary over-feeding in the short term that rapidly returns to its normal pattern. It has been recently demonstrated in an elegant study with genetically programmed and rescued mice that chronic overweight leads to secondary adaptations which act to perpetuate obesity despite reductions in caloric intake [10]. Individuals who lose weight have lower energy expenditure and increased hunger compared to individuals with the same weight that never weighed more [9, 11]. With all the published data in the field, it is easy to understand why lifestyle intervention obtains very weak results which are not sustained long term. Generally, weight loss of between 5 and 10 % is considered effective and is able to reduce several risk factors and comorbidities associated with excessive weight.

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A recent meta-analysis that organized data from 21 clinical trials (after a review of more than 6,000 abstracts and 600 articles) showed a placebo subtracted weight loss (without lifestyle intervention or with standard lifestyle intervention compared to an intensive one) of only 3.01 kg (or an average of 4 % weight loss) in 12–18 months [12]. Although the difference was significant and the author concludes that lifestyle intervention was effective, the result is quite disappointing, especially for patients desire.

When we analyze subgroups of patients that lose more than 5 %, or more than 10 % of their weight, the result depends on the intensity of the lifestyle intervention. In a recent study in primary care practice that compared usual care, brief lifestyle intervention and enhanced lifestyle intervention (which is very difficult to do outside clinical trials and sometimes involved the use of the medication orlistat) the 5 % weight loss was 21.5 %, 26.0 %, and 34.9 % after 2 years and the 10 % weight loss was 6.2 %, 9.9, and 17.8 % [13]. This data suggests that it is possible to lose weight with lifestyle modification programs on an individual basis, but it is still clearly far from being a perfect treatment for the majority of obese subjects and for epidemiological changes in the rates of obesity worldwide.

To lose and maintain weight on a long-term basis is so challenging, that the USA has a National Weight Control Registry which maintains data of nearly 5,000 individuals who have successfully achieved a substantial weight loss of at least 16 kg [14]. The major characteristics of these individuals are: consumption of low-energy, low-fat diets; engaging in high levels of physical activity, consistent self-monitoring of body weight and food intake; eating breakfast regularly; and demonstrating a high level of dietary restraint. These individuals have recently been divided in four big clusters, with different characteristics [14].

## Type of Diet

Much controversy exists regarding whether the macronutrient content of a diet is more important

than its caloric content, with regard to weight loss. Much is known about the cardiovascular benefits of the Mediterranean Diet, for example, but there is no strong evidence that this, or any diet, is more effective for weight loss than others [15, 16].

Low-carbohydrate diets lead to more accentuated weight loss in the first months, but after 1 year the difference is no longer significant. This type of diet is also more difficult to maintain in the long-term and can lead to adverse reactions such as headache, fatigue and irritation, due to ketosis [15, 16].

A recent comparison of weight loss diets with different compositions of fat, protein and carbohydrates concluded that reduced-calorie diets result in clinically meaningful weight loss, regardless of which macronutrients they contain. Satiety, hunger, satisfaction with the diet and attendance at group sessions were similar for all diets. The diets improved lipid risk factors and fasting insulin levels in the directions that would be expected on the basis of macronutrient content [15, 16].

In summary, the best diet is one that fits better individually and in which the caloric content is more important than the macronutrient content.

Very-low calorie diets (<800 kcal/day) can achieve more weight loss in the short term, but do not produce greater weight loss than conventional low calorie diets and their use should be limited to specific situations which demand rapid weight loss (e.g., before nonurgent abdominal surgery), on an individual basis [17].

## Physical Activity

Physical inactivity has recently been compared to smoking as an enormous hazard for human health [18]. It was demonstrated that it caused 9 % of premature mortality worldwide, or more than 5.3 million (versus 5.1 million from smoking) of the 57 million deaths that occurred in 2008. If it was possible to eliminate physical inactivity in the world, the life expectancy of the world's population would increase by 0.68 years.

In respect to weight loss, exercise has a more limited role. Exercise alone, when not combined

with diet, generally has a minimal effect on weight. In a meta-analysis the mean difference of exercise compared with no treatment was 1.6 kg [19]. However, exercise is often associated with reductions in total body fat, visceral fat, insulin resistance, blood pressure and elevations in HDL-cholesterol.

Programs which combine physical activity and diets generally have limited efficacy when compared to diet-only programs in the short term, mainly because the energy expended in a moderate exercise program is far less than the possible energy saved by a traditional diet. However, compared to diet-only programs, the diet-plus-exercise programs provide greater long-term weight loss maintenance [20].

Obese individuals are normally recommended to exercise for 150–250 min a week (30–50 min, 5–7 times a week). However (although not analyzing weight) it was demonstrated that 15 min of physical activity per day is associated with reduced mortality [21] and even 10 min of intermittent vigorous and moderate physical activity three times a week is capable of improving metabolic surrogates and fitness [22]. Because many obese individuals are sedentary, smaller prescriptions of physical activity could improve adherence and lead progressively to traditional recommended goals.

In respect to the type of physical activity, aerobic treatment is more efficient than resistance training in promoting weight loss and cardiometabolic health and, if time commitment is a problem, should be the first choice in an obese individual [23]. Aerobic training reduces body weight and measures of visceral fat and fatty liver infiltration and also improves fasting insulin resistance and liver enzymes.

Finally, although obesity is associated with excess mortality in several epidemiological studies [24], a recent article found that, adjusted for fitness, metabolically normal obese individuals have the same all-cause mortality as normal weight individuals, suggesting that even if obese individuals cannot normalize their weight, physical activity still has several health benefits for them and can limit the burden of their chronic disease [25].

## Other Lifestyle Approaches

Obesity is associated with several other factors, of which some can be modified and some not. Alcohol consumption, excessive stress, short and long sleep, shift work, excessive light at night, excessive television watching, air-conditioning, living near busy roads, pollution, endocrine disruptors, having obese friends (more than partners), intestinal microbiota, viral infections, smoking cessation, and use of medications (mainly psychiatric), among many others [6]. An extensive clinical anamnesis is important for recognizing some of these factors and modifying them, if possible.

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## Medications

When considering drug treatment for obesity, some aspects must be discussed: pharmacological treatment is only justified when combined with diet and lifestyle intervention; pharmacological treatment does not cure obesity—when discontinued, weight regain normally occurs; antiobesity medications should be used under continuous medical supervision; drug choice should be decided on an individual basis—one size does not fit all: eating habits, comorbidities, safety profile, other medications in use, initial response and other subjective analysis help make the decision; treatment should be maintained only when it is considered safe and effective for the aforementioned patient.

Pharmacological treatment is indicated when BMI is over 30 kg/m<sup>2</sup> or if comorbidities likely to improve if weight loss occurs are present with a BMI of over 25 kg/m<sup>2</sup>, after lifestyle interventions have proved unsuccessful.

Unfortunately, there are very few options of antiobesity drugs currently available, in contrast to vast number of medications available for the treatment of diabetes and hypertension and despite the increasing knowledge of the pathophysiology of obesity in the last decades. This lack of options is possibly due to all the metabolic adaptations that complicate weight loss and can neutralize the effects of medications, and the pos-

sible harm of medications that heighten energy expenditure via sympathetic activation, but also because there is still a misconception, mainly from Regulatory Agencies, that obesity is not a real disease and its treatment, relying on lifestyle modification, is much simpler than it really is.

Orlistat is the only approved antiobesity drug in Europe. In the USA, catecholaminergic agents such as phentermine and diethylpropion are also approved, but only for short-term treatment (12 weeks), although are often used for much longer periods. Interestingly, in the USA, the FDA went 13 years without approving new drugs for the treatment of obesity after the approval of orlistat back in 1999. In addition, it withdrew sibutramine (which is still available in Brazil) from the market in 2010, the most studied antiobesity drug to date, due to cardiovascular safety concerns raised by adverse outcomes observed in the SCOUT trial, which enrolled only high-risk patients [26]. Fortunately, in 2012 two new drugs were approved in the space of less than a month and it is believed that this represents a change of thinking from FDA, which influences decisions of several other regulatory bodies around the world.

Besides the on-label medications, there are other drugs that cause weight loss and are frequently used for off-label treatment. Combinations of antiobesity drugs are also considered off-label (with the exception of the recently FDA-approved phentermine/topiramate fixed dose in a single pill), but are widely used in clinical practice.

Moreover, in a questionnaire conducted with obesity specialists in the USA, 85 % of them reported prescribing combination of drugs and 65 % admitted to prescribing drugs not currently approved for the treatment of obesity [27].

In this section, we will focus on the available on-label medications, but also briefly mention the off-label options, combinations and drugs being developed.

## Orlistat

As previously mentioned, orlistat is the only approved weight-loss drug in Europe and prior to

the recent approval of lorcaserin and phentermine/topiramate (see below) by the FDA, was the only long-term option in the USA.

Orlistat is a synthetic hydrogenated derivative of lipstatin, produced by the fungus *Streptomyces toxytricini*. It partially inhibits gastric lipase, pancreatic lipase and carboxyl ester lipase enzymes. These enzymes work by hydrolyzing the dietary triglycerides into fatty acids and monoglycerides, which are subsequently absorbed by the mucosal cell of the gastrointestinal (GI) tract. Orlistat reduces the absorption of ingested fat by 30 %, increasing its excretion in the feces. It has the potential advantage of not being absorbed in doses up to 800 mg/day, more than double the prescribed dose of 360 mg, so it does not affect the neuronal circuits regulating appetite [28].

By reducing fat absorption by 30 %, orlistat helps individuals on a diet to reduce their daily calorie intake. In individuals on a balanced diet containing no more than 30 % fat, it will have a small effect in the short-term, but the energy deficit due to reduced fat absorption on a longer basis can be highly significant. Orlistat also helps individuals to reduce the fat content of their diet, as diets rich in fatty products will lead to more adverse effects, basically diarrhea, flatulence and fecal incontinence [28].

The results in weight-loss trials with orlistat have been positive, but not impressive. A recent meta-analysis resulted in a weight loss of 5–10 kg (8 % of baseline weight) compared with 3–6 kg (5 % of baseline weight) for placebo [12]. All orlistat trials used intensive behavioral components and this explains the significant weight loss seen in the placebo group. In categorical analysis, 5 % and 10 % weight loss were seen in 55 % and 26 % of individuals using orlistat versus 33 % and 14 % with placebo [29].

Orlistat is also associated with a significant reduction in systolic and diastolic blood pressure compared to placebo (−4.9 vs. −2.4 mmHg and −3.7 vs. −1.8 mmHg, respectively,  $p < 0.05$ ). Individuals with isolated systolic blood pressure (>140 mmHg) have even better benefits, with reductions of up to 10.9 mmHg [30].

Orlistat is also beneficial in regard to glucose control, even when weight loss is not successfully

**Table 41.1** Studies using orlistat

References	$\Delta t$ week	$n$ (P/O)	Dose (mg/day)	$\Delta$ weight (P)	$\Delta$ weight (SA)	Comments
[55]	12	19/20	150	-2.1 kg	-4.3 kg	First clinical study
[56]	12	39/37	30	-3.2 kg	-3.6 kg	Different dosages
		39/45	180	-3.2 kg	-3.9 kg	
		39/47	360	-3.2 kg	-4.8 kg	$\Delta$ weight SS $p < 0.01$
[57]	24	136/134	90	-6.5 %	-8.5 %	NS; different dosages
		136/135	120	-6.5 %	-8.8 %	$\Delta$ weight SS $p < 0.002$
		136/136	360	-6.5 %	-9.8 %	$\Delta$ weight SS $p < 0.002$
		136/135	720	-6.5 %	-9.3 %	$\Delta$ weight SS $p < 0.002$
[58]	52	23/23	360	-2.6 %	-8.4 %	$\Delta$ weight SS $p < 0.001$
[59]	52	113/115	360	-5.4 %	-8.5 %	
[60]	52	186/1 O	360	-4.6 %	-5.9 %	Coronary risk
[52]	104	343/345	360	-6.1 %	-10.2 %	$\Delta$ weight after 1 year
[50]	104	223/657	360	-4.5 %	-7.6 %	$\Delta$ weight SS $p < 0.001$
[61]	104	265/266	180	-4.1 kg	-7.1 kg	$\Delta$ weight after 1 year
		265/264	360	-4.1 kg	-7.0 kg	
[64]	104	243/242	180	-6.6 %	-7.6 %	$\Delta$ weight after 1 year
		243/244	360	-6.6 %	-9.7 %	
[62]	104	316/35	360	-3.8 kg	-6.7 kg	IGT progression
[63]	104	36/36	360	-8.6 kg	-13.1 kg	
[53]	52	159/162	360	-4.3 %	-6.2 %	Diabetics SS $p < 0.001$
[54]	24	174/164	360	-3 %	-4.7 %	Diabetics SS $p < 0.001$

SA orlistat,  $t$  study duration,  $w$  week,  $P$  placebo,  $NA$  not available,  $IGT$  impaired glucose tolerance,  $NS$  not significant,  $SS$  statistically significant

achieved. In the XENDOS study it was demonstrated that orlistat is able to reduce the incidence of diabetes in individuals with the metabolic syndrome and it has beneficial weight-independent effects on blood glucose and HbA1c. A weight independent reduction in LDL-cholesterol is also seen in patients using orlistat and it could be a good alternative for patients that do not tolerate statins. It is postulated that orlistat can also reduce the progression of nonalcoholic steatohepatitis [31].

Table 41.1 summarizes some of the studies with orlistat [32].

The main adverse effects of orlistat are gastrointestinal in nature and include diarrhea, flatulence and fecal urgency and incontinence. In May 2010, the FDA issued a drug safety communication about a possible relationship between the product and isolated cases of severe hepatic insufficiency (13 cases), with three hepatic transplants and two deaths. There is no pharmacokinetic explanation for these cases. Another adverse effect recently published has been acute kidney

injury (AKI) induced by oxalate. A 2 % increase in AKI was demonstrated in a revision of 953 patients [33]. The malabsorbed fat is able to bind to enteric calcium, increasing free oxalate absorption and leading to hyperoxaluria, a risk factor for kidney stones. The poor fat absorption is also likely responsible for serum level reductions of liposoluble vitamins (A, D, E, and K) and could reduce the absorption of some medications.

Orlistat 120 mg is given three times a day, at breakfast, lunch, and dinner. In Brazil and other countries in which breakfast is much smaller than lunch and dinner, a twice daily dose is acceptable. With our experience in the management of obesity, we consider orlistat a good choice of treatment for hyperphagic patients (who eat proportionally more total calories and fat in meals than in snacks); for patients on weight maintenance regimens after weight loss; and for individuals with high LDL, NASH or a high risk of diabetes. We also consider the drug in combination (see below).

## Sibutramine

Sibutramine is the most studied antiobesity drug, but it was withdrawn from the market of the vast majority of countries due to the SCOUT Study, although still available in Brazil upon special medical order [26].

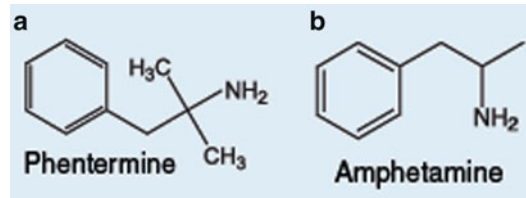
It was obtained after modifications in the chemical structure of amphetamine, being considered a beta-phenethylamine derivative. Sibutramine acts by blocking norepinephrine and serotonin uptake in the synapsis, leading to a reduction in food intake by increasing satiety. An increased thermogenesis was also demonstrated in mice [34].

In a meta-analysis, the placebo subtracted weight loss was 4.2 kg (4.3 %) with sibutramine. In addition, sibutramine treatment increased the absolute percentage of 5 % and 10 % responders by 32 % (55 % vs. 27 %) and 18 % (28 % vs. 10 %), respectively [29].

Treatment with sibutramine significantly reduces waist circumference and triglyceride concentration and increases concentrations of HDL-cholesterol. LDL-cholesterol was not significantly reduced and glycemic indexes only reduced in those who lost more weight [35].

The main adverse effect is an increase in sympathetic tone, which leads to a small increase in pulse and blood pressure. Due to this effect, the drug was always contraindicated in subjects with established cardiovascular disease.

The SCOUT Study (Sibutramine Cardiovascular Outcomes Trial) was designed to assess the cardiovascular safety of the drug and was conducted in a high-risk population (diabetic patients with one or more risk factors for CVD, previous history of CVD and diabetic with established CVD) [26]. A discrete, but significant, increase in nonfatal cardiovascular events was observed in the intervention group (11.4 %) compared to placebo (10 %). This 16 % increases lead the EMEA (European Medicine Agency) to withdraw sibutramine from the European Market. Afterwards, Abbott (who have the commercialization rights of the drug in the USA) voluntarily withdrew the drug from the North-American market before an official statement from the FDA, but the drug never achieved



**Fig. 41.1** Molecular structure of phentermine and amphetamine

popularity in that country. In Brazil, the drug still is sold, but with severe restrictions for its prescription and acquisition made by ANVISA, Brazil's local regulatory agency.

A sub-analysis of the SCOUT report recently suggested that modest weight loss over short-term and long-term periods was associated with reductions in subsequent cardiovascular mortality for the following 4–5 years, even in those with preexisting cardiovascular disease [36]. The increased nonfatal cardiovascular events observed in the overall analysis probably represent individuals who did not achieve weight loss, but persisted in the intervention group due to the study design, something that does not happen in clinical practice.

The drug should not be used in combination with other serotonin uptake inhibitors, like many antidepressants, due to a risk of serotonergic syndrome, a very rare but potentially severe condition.

## Catecholaminergic Agents: Phentermine and Diethylpropion

Phentermine is an amphetamine analogue which promotes weight loss, acting as an appetite suppressant that interacts with amine transporters in the central nervous system (Fig. 41.1) [37]. Its main action is in the norepinephrine transporter, leading to a greater release of norepinephrine in the synapsis. It also has a weak activity in the dopamine transporter and an even weaker one in the serotonin transporter. The drug has been approved for the short-term treatment of obesity since 1959 and is the most widely prescribed anti-obesity medication in the USA, and was even prior the withdrawal of sibutramine. As it was approved long before the modern rules and regulations for

drug marketing and is a very cheap medication with no patent owner, long-term clinical trials were never conducted. A meta-analysis of its safety, analyzing six randomized trials, showed a modest placebo-subtracted weight loss of 3.6 kg, with large heterogeneity between the studies, with lengths ranging from 2 to 24 weeks [38]. The main adverse effects are anxiety, insomnia, and sympathetic activation (a rise in blood pressure and tachycardia) and the drug is contraindicated in people with underlying cardiovascular disease and severe psychiatric conditions. Contrary to what many physicians believe, due to the chemical resemblance with amphetamine there is limited dependence liability with this medication (FDA DEA schedule IV). In current clinical practice in the USA, any use of phentermine for longer than 12 weeks is considered off-label and the drug is unavailable in several parts of the world, such as in Brazil and Europe.

Recently, the combination of phentermine with the antiepileptic drug topiramate has been approved in the USA for long-term obesity treatment (see below).

Diethylpropion has a similar mechanism of action, as well as indications and contraindications, to phentermine [39]. It is also poorly studied and less prescribed than phentermine.

## Lorcaserin

Lorcaserin is a selective serotonin receptor (5-HT<sub>2C</sub>) agonist with a much greater 5-HT<sub>2C</sub> selectivity, than 5-HT<sub>2b</sub> [40]. This specificity appears to be important in reducing the risk of valvulopathy detected with similar older compounds such as phenfluramine, withdrawn from the market in 1997 (used in a fixed dose combination with phentermine) after 24 reports of valvular dysfunctions in individuals on continued use of this drug, as cardiac valves have mainly the 5-HT<sub>2b</sub> subtype [41].

The serotonergic stimulus activates the POMC system and diminishes caloric intake while increasing catabolism via second-order effectors, such as TRH, CRH and MC4R [42]. Some human studies have detected an increased basal meta-

bolic rate and thermogenesis, but this result was not reproducible in all experiments.

The most studied dose was 10 mg bid [40]. A phase three study, BLOOM, randomized 3,182 obese subjects (BMI 30–45 kg/m<sup>2</sup> or 27–30 kg/m<sup>2</sup> with obesity-related comorbidities). The placebo-subtracted weight loss was 3.6 % (5.8 % vs. 2.2 %) and the 5 % weight loss was 47 % compared with 20 % in placebo. More patients also lost 10 % or more of their baseline body weight in the lorcaserin group than in the placebo group (22.6 % vs. 7.7 %) [40].

The rate of cardiac valvulopathy was not increased with the use of lorcaserin after serial echocardiography analysis. The most frequent adverse events reported were headache, dizziness, and nausea, with similar rates of serious adverse events compared to placebo. The FDA approved lorcaserin after more than 13 years since its last antiobesity drug approval.

Although the results were only reasonable, we think lorcaserin could be a good option for patients who cannot use or tolerate other drugs.

## New Drugs

There are several research projects on the development of new drugs for obesity treatment. To date, tesofensine, a serotonin–norepinephrine reuptake inhibitor and cetilistat, a drug with similar mechanisms than orlistat, are the most advanced, in phase two studies [32, 43]. See Table 41.2.

## Off-Label Drugs

As cited before, a substantial number of obesity specialists in the USA (and around the world) admitted to prescribing off label medications for weight loss [27]. We will briefly describe the most commonly used drugs for the treatment of obesity that are not officially approved for such use.

## Topiramate

Topiramate, a monosaccharide D-fructose derivative, is an antiepileptic and migraine prophylaxis drug that commonly results in weight loss [44]. Its

**Table 41.2** New perspectives for obesity treatment

Drugs	Studies	N	Weeks	Placebo subtracted weight loss (%)
Lorcaserin (FDA-approved)	BLOOM (phase 3)	3,182	52	3.6
	BLOSSOM (phase 3)	4,008	52	3.1
Phentermine + Topiramate (FDA-approved)	EQUIP (phase 3)	1,267	56	9.4 (higher dose)
	CONQUER (phase 3)	2,487	56	8.6 (higher dose)
Tesofensin	TIPO-1 (phase 2)	203	24	9.2 (0.5 mg)
Liraglutide	Phase 2	564	20	4.5 (3.0 mg)
Cetilistat	Phase 2	612	12	1.3 (120 mg)
Bupropion + Naltrexone	COR-I (phase 3)	1,742	60	4.8
	COR-II (phase 3)	1,496	60	5.2
Bupropion + Zonisamide	(Phase 2)	320	24	6.1
Pramlintide + Metreleptin	(Phase 2)	139	24	–

mechanisms of action are not fully understood and are very complex, involving many pathways. It enhances GABAergic activity via chloride channels, antagonizes NMDA-glutamate receptors, blocks voltage-dependent sodium channels, and also weakly antagonizes carbonic anhydrase isoenzyme subtypes II and IV [44]. The exact mechanisms by which all these actions promote weight loss are speculative, but clinically it has been shown to have a great impact in reducing binge-eating episodes and cravings, eating behaviors which affect a substantial percentage of obese individuals [45]. More recently, it has been proposed that topiramate exerts its effects on weight by improving hypothalamic leptin and insulin signaling and action [46]. The same study, on rodents receiving topiramate, found an increase in anorexigenic peptides and improved energy metabolism in peripheral tissues due to AMPK-signaling.

A large number of placebo-randomized trials have evaluated the efficacy and safety of topiramate as a long-term weight-loss drug. A recent meta-analysis of ten randomized trials confirmed a significant placebo-subtracted weight loss of 5.34 kg and a sixfold increased chance of significant weight loss (5 % or 10 %), although dosages varied considerably [47]. The largest study conducted over 60 weeks used dosages of 96, 192, and 256 mg, with mean percentage weight losses of 7.1 %, 9.1 %, and 9.7 %, respectively (versus 1.7 % in the placebo group) [48]. Other advantages of topiramate include the lack of a weight plateau during the first 6-months of treatment and a favorable metabolic profile, with reductions in

insulin resistance, glucose intolerance and blood pressure [47], with positive results also observed in the type 2 diabetic population. The drug was also tested in obese patients with binge-eating disorders, with a reduction of binge-eating scores and weight loss [45]. The main disadvantage of the drug is its adverse effect profile that leads to significant discontinuation rates, mainly due to paresthesias, memory/concentration impairment, and somnolence [48]. Nevertheless, severe adverse effects are rare and include nephrolithiasis, due to its carbonic anhydrase inhibition activity. This drug was never submitted for approval for obesity monotherapy, but has recently been used in a fixed-dose combination with phentermine (see below).

### GLP-1 Analogs (Liraglutide and Exenatide)

GLP-1 analogs are antidiabetic drugs which frequently result in weight loss [49]. Due to this effect, these drugs are considered an excellent option for obese type 2 diabetic individuals. In the obese nondiabetic population, these drugs have also been studied in phase 2 studies, mainly liraglutide, with fairly good results, but have not yet been approved [50].

Liraglutide has 97 % structural homology with native GLP-1, but with a significantly larger half-life (13 h vs. 2 min) which allows a once daily regimen [49]. It leads to weight loss due to GLP-1 action in the gastrointestinal tract, reduc-



ing gastric emptying and promoting gastric distention which together increases satiety and satiation, but also acts on the CNS through its specific receptors, with not fully recognized mechanisms involving reduced energy intake and reduces the hedonic drive to eat [49].

The dosages used in phase 2 randomized-controlled trials for obesity are bigger than those for diabetes (up to 3.0 mg daily) [50]. After 1 year, the 3.0 mg dosage was associated with a placebo-subtracted weight loss of 4.5 % (7.2 kg vs. 2.8 kg) and 5 % and 10 % weight loss of 61 % vs. 29 %. The drug was also compared with orlistat and achieved better results (3.1 kg more weight loss and 32 % more 5 % weight-loss responders). Although 3.0 mg is not approved, doses of 1.8 mg were also superior to orlistat and the 1.2 mg dosage was similar. After 2 years, the results were sustained and the prevalence of prediabetes and metabolic syndrome decreased by 58 % in the 3.0 mg dose, with improvements in blood pressure and lipids. The biggest side effects were nausea and vomiting, mostly transient and dose-dependent. Although animal models suggested an increased prevalence of medullary thyroid cancer in rats receiving the drug, this is almost certainly not relevant to humans due to a lack of GLP-1 receptor expression in thyroid c-cells compared with an abundance in rodents [51].

We expect phase-3 study results to reproduce these good results, leading to an approval for its use in nondiabetic populations in the next few years.

Exenatide has a similar mechanism of action but is routinely used twice daily due to its shorter half-life and higher peak values [52]. Apparently, it has a similar adverse effect profile, but a smaller weight reduction, although few head-to-head data are available.

## Metformin

Metformin, the most-prescribed antidiabetic drug worldwide has a favorable weight profile in this subpopulation. However, the small weight reduction observed with metformin does not make it suitable purely for weight loss, although its use is associated with diabetes reduction risk in the prediabetic population, as seen in the DPP study

[53]. Metformin has also been studied in obese children and adolescents, and can be a good option for reducing risk factors [54].

## Fluoxetine and Sertraline

Both selective serotonin reuptake inhibitors are antidepressants commonly used for depressive obese individuals. They are not, however, efficient weight-loss medications since the initial weight loss commonly observed is not sustained on a long-term basis, even with continued use [55]. They can be useful for eating disorders such as *bulimia nervosa*, binge-eating disorder and night eating syndrome as they can reduce compulsive episodes, but the management of these conditions is not within the scope of this chapter.

## Bupropion

Bupropion is a norepinephrine and dopamine reuptake inhibitor used mainly for the treatment of depression and smoking cessation [55, 56]. It is proposed that the increased levels of dopamine and norepinephrine in the arcuate nucleus may trigger POMC neuron signaling and lead to appetite suppression [57]. Bupropion alone was studied for the treatment of obesity with a placebo subtracted weight loss of 3–5 kg with an early plateau. This plateau can be explained by a compensatory feedback, with an increased production of beta-endorphin [56].

It has recently been studied in combination with naltrexone (see below) [57].

## Combination of Drugs

Before the recent approval of the phentermine/topiramate fixed dose combination, any combination of drugs for the treatment of obesity was considered *off-label*. It appears, however as an interesting option for its treatment, as we know that it is a multifactorial disease, with linked environmental and genetic factors and redundant pathways that make it difficult to obtain sustained weight loss.

Our group has recently reviewed the possible advantages and disadvantages of combination therapy for the treatment of obesity [58]. Due to

synergic or addictive effects it may have increased therapeutic efficacy; it may block compensatory mechanisms that leads to a weight loss plateau; and the potential use of lower doses could minimize adverse effects. Possible disadvantages include costs, drug interactions, and dosage inflexibility (when the combination is in the same pill).

### Phentermine and Topiramate Fixed Dose Combination

The rationale for the combination therapy of phentermine and topiramate stems from the good efficacy of both drugs combined with a significant, but very different, profile of adverse effects. As previously cited phentermine can have sympathetic and stimulant effects, as topiramate is more sedative and also reduces blood pressure. In conjunction, both drugs can have additive effects on weight, thus reducing dosages, side effects, non-desired reactions, and discontinuation rates [59].

After good preclinical and clinical studies, a phase 3 trial (CONQUER) evaluated 2,487 individuals over 56 weeks with BMI from 27 to 45 kg/m<sup>2</sup> and at least two of the following comorbidities: hypertension, dyslipidemia, diabetes or prediabetes, and abdominal obesity [60]. They were blindly randomized into three groups: placebo, P7.5/T46, and P15/T92 [10]. The median weight loss in absolute and percentage change was 1.4 kg (1.2 %), 8.1 kg (7.8 %), and 10.2 kg (9.8 %), respectively. Patients that completed 1 year of treatment had a mean weight loss of 9.9 kg in the lower dose and an impressive 12.9 kg in the higher dose, making this combination the most potent weight loss drug ever studied in a phase III trial. The percentages of individuals that achieved 5 and 10 % weight loss with placebo, P7.5/T46, and P15/T92 were 21 %/7 %, 62 %/37 %, and 70/48 %, respectively.

It also showed benefits in risk factors, such as glycemia, lipids, and blood pressure and a low dropout rate compared to other weight-loss trials.

An extension Study (SEQUEL Study) evaluated a subgroup of the original participants and observed sustained results with continued use [61].

The most common side effects most significantly related to the drug were dry mouth,

paresthesia (the leading cause of discontinuation), constipation, dysgeusia, insomnia, and dizziness, with a dose-dependent pattern. Anxiety and irritability were reported by approximately 4 % of the intervention group versus 2 % in the placebo group. Disturbance in attention was also reported in 4 % of the higher dose group against 2 % in the lower dose and less than 1 % in the placebo group. An increased heart rate of 1.7 beats per minute was seen in the higher dose group, consistent with phentermine's sympathetic activation. Nephrolithiasis was significantly more frequent in the higher dose group with a 1 % incidence (11 individuals), but there was no difference to blurred vision (a concern with topiramate) between the two intervention groups and placebo [60, 61].

The combination was approved by the FDA in 2012, but post-commercialization surveillance and a long-term trial to better assess the safety profile data were demanded. It is hoped this will be an excellent option for obesity treatment.

### Bupropion–Naltrexone Fixed-Dose

Bupropion has already been described and naltrexone is an opioid antagonist drug approved for the treatment of opioid and alcohol dependence [62]. Ever since 1979 when naloxone, a classical opioid antagonist, induced a significant reduction in food intake in mice, it has been proposed that opioids have a role in appetite regulation.

Although some reports commented on a possible decrease in food intake and weight loss with naltrexone, its use as monotherapy in obesity is not associated with significant weight loss [63]. However, knowing the mechanisms of action of both drugs, it was cleverly proposed that an inhibition, mediated by naltrexone, of the autoinhibition of a bupropion-stimulated POMC pathway could result in better and more sustained weight loss than either drug alone [57].

After preclinical and clinical studies, phase 3 studies were designed accordingly, using a daily dose of 16 and 32 mg/day SR naltrexone and 360 mg SR bupropion, divided into a twice-daily basis [64].

The COR-I (Contrace Obesity Research-I) trial randomized 1,742 patients for NB16, NB32 or placebo, with a 4 week titration period followed by 56 weeks of treatment (29). The placebo-subtracted weight loss was 3.7 and 4.8 % for NB16 and NB32, respectively. In the NB32 group, 48 %, 25 %, and 12 % of the patients lost more than 5 %, 10 %, and 15 % respectively, compared with 39 %, 20 %, and 9 % with NB16 and 16 %, 7 %, and 2 % in the control group. The most commonly observed side effect was nausea, around 30 %, compared to 5 % and 6 % in the placebo group. The incidence occurred mainly in the initial weeks of treatment, still within the titration phase, with a tendency to fall after the fourth week. Other side effects that were significantly more common than for placebo, in order of frequency were: constipation, headache, dizziness, vomiting and dry mouth. There was no significantly higher incidence of adverse effects on the cardiovascular system, nor in relation to depressive disorders or suicidal ideation [64].

The combination was initially approved by the FDA Advisory Committee in 2010 but surprisingly rejected by the FDA afterwards, as they demanded more safety data regarding cardiovascular effects. This data along with reassessment from the FDA are eagerly awaited.

### Other Fixed-Dose Combinations Being Studied

Pramlintide/metreleptin, bupropion/zonisamide, pramlintide/phentermine, GLP-1/PYY 3-36, and others are being studied at different phases. We anxiously expect for its results [32, 43].

### Sibutramine and Orlistat

This is one of the few combinations that have been studied in clinical practice; the results of which were generally poor.

Two studies were conducted at different centers in Turkey, with similar results [65, 66]. In a 12 week randomized open-label study, treatment with diet alone ( $n=19$ ) was compared with diet

combined with the use of sibutramine ( $n=22$ ), orlistat ( $n=25$ ) and sibutramine combined with orlistat ( $n=20$ ) [27]. The combination of sibutramine and orlistat proved more effective in the reduction of BMI compared to monotherapy with orlistat ( $p<0.001$ ), but not significantly superior to sibutramine alone. Placebo-subtracted weight loss of the combined therapy was 6.5 % (13.4 % combination vs. 6.9 % placebo).

Another study involving 89 obese women, showed a mean weight loss of 5.5 %, 10.2 % and 10.6 % with orlistat alone, sibutramine alone and combined therapy respectively. Again there was no statistical difference between the latter two groups. Despite these disappointing results, around 14 % of obesity specialists are reported to have used this combination in clinical practice [27].

A large clinical series done by our group was developed to evaluate the efficacy of the combination of sibutramine and orlistat in 446 individuals for 6 months, with concomitant dietary counseling [67]. Weight loss at 3 and 6 months was 9.9 and 13.4 % for women and 8.7 and 12.3 % for men. After 6 months, 88.7 % of the patients that finished the study had lost more than 5 % of baseline weight and 66 % had lost more than 10 %. The rate of discontinuation was 37 %. Although an open-label study, not only the numbers of patients enrolled were considered to be expressive but also the proportion of patients with significant weight loss.

It is our belief that this combination appears to provide satisfactory results, although this was not confirmed in randomized controlled studies. In contrast with our opinion, some specialists in the field of obesity believe that concomitant use of drugs acting on the gastrointestinal tract with centrally acting drugs does not result in additional weight loss compared to the latter by itself [58].

### Other Combinations

Although commonly used, other combinations of on-label and off-label obesity drugs have not been studied in clinical trials, with few exceptions such as one study with metformin and orlistat [68].

## Conclusion of Pharmacological Therapy

Despite the increasing prevalence of obesity, a chronic and potentially deadly disease, its treatment is far from being ideal, relying mainly on lifestyle modifications that offer very limited long-term efficacy. Pharmacological therapy does not preclude lifestyle modification and it is more effective than the latter alone. With specialist long-term surveillance, it is safe and although it will certainly not solve obesity problems worldwide, it can help a good fraction of the obese population to improve their health, quality of life and self-esteem. It is believed that obesity, as well as other common chronic diseases such as type 2 diabetes, hypertension and asthma, should be treated chronically and with drug combinations, if necessary.

Fortunately, new drugs are being developed and combinations of existing ones are being studied. Regulatory agencies that for years closed their eyes to the problem, by banning and not approving some possibly helpful drugs, recently seem to be more concerned and in less than a month the FDA has approved two new drugs for the treatment of obesity.

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## Medical Versus Surgical Treatment

Surgical procedures are becoming increasingly common. Registers from 2003 through 2008 in North America documented that the number of bariatric operations in the USA peaked in 2004 at 135,985 cases and plateaued at 124,838 cases in 2008 [69].

Bariatric surgery appears as a useful way of promoting effective weight loss in patients that still have a high body mass index refractory to lifestyle modification and drug therapy and for those with complications secondary to the elevated body mass index. It also results in a greater decrease in cardiovascular risk factors and achieves higher remission of type 2 diabetes. Among all obesity therapies (lifestyle modification and pharmacotherapy), it is the only proven therapy that can reduce mortality in obese patients [70].

Classical surgery indications are:

- BMI > 40 kg/m<sup>2</sup>  
or
- BMI 35–39.9 kg/m<sup>2</sup> with one or more severe complications of obesity (such as type 2 diabetes mellitus, hypertension, sleep apnea) and
- Inability to maintain weight loss with conventional therapy
- Have an acceptable risk for surgery and be well prepared and motivated

Due to high success rates, it has been proposed that surgery should also be an option for lower BMIs and the endoscopic intragastric balloon (see below) has recently been approved for this population.

Surgical procedures can be divided in three groups: restrictive, malabsorptive or mixed.

The restrictive mechanisms consist of limiting caloric intake by restricting stomach size via resection, bypass or by physically restricting the passage of food. At first glance, these procedures tend to have simple techniques and often result in clinically significant weight loss, making them the first choice for many patients and physicians.

The malabsorptive procedures consist of altering the passage of food to the small intestine promoting a reduction in the amount of nutrients the body can absorb, generally by shortening the surface area of the small bowel, by bypassing it or by diverting the biliopancreatic secretions that facilitate absorption [71].

We should note, however, that any surgery that rearranges the gastrointestinal tract also alters some hormonal dynamics (such as GLP-1, PYY, CCK, and ghrelin, among others associated with peripheral control of appetite). This rearrangement can be highly responsible for the weight loss and long-term maintenance, as well as for the improved metabolic outcomes, that include long-term diabetes prevention (in pre-DM individuals) and diabetes remission among subjects already diagnosed with the disease [72].

A successful surgical procedure is defined as a long-term weight loss of more than 50 % of the excess weight (the difference between the actual weight and the ideal individual weight) or

decreasing and maintaining the BMI below stage III obesity ( $\text{BMI} < 40 \text{ kg/m}^2$ ).

The surgical risk and clinical complications have been progressively reduced with the improvement of the different techniques. The creation and advance of the laparoscopic approach has had a relevant impact on common surgical complications such as wound infection and incisional hernias, it reduces hospital stay, clinical complications and lowers the mortality rates compared with open surgery when performed by experienced hands [73].

The more relevant procedures are summarized here:

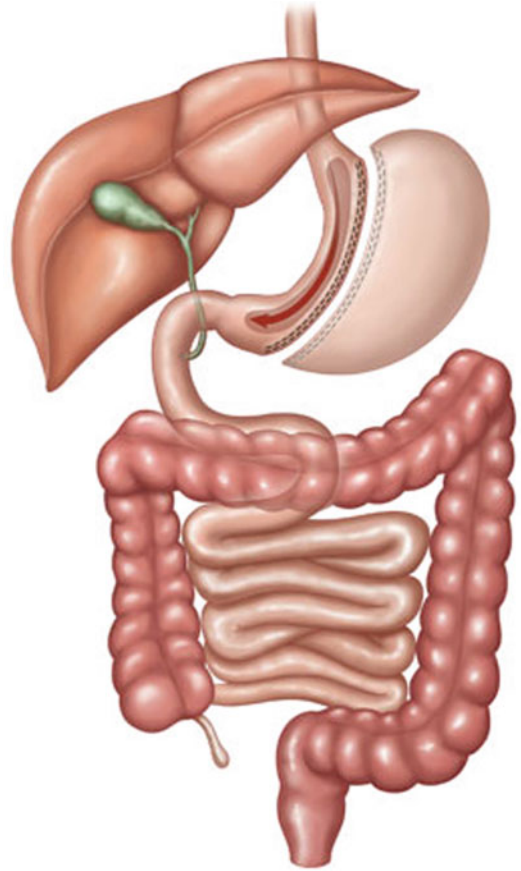
*Laparoscopic adjustable gastric banding (LAGB)*

A silicon band is placed laparoscopically around the proximal part of the stomach—cardia, creating a small pouch with 20–30 ml of volume with physical resistance to food intake. The band can be adjusted by inflating or deflating a balloon connected to a port which is placed subcutaneously and can be easily accessed percutaneously, modulating the degree of restriction [74].

The minor extension of the surgical procedure promotes lower mortality rates and lower peri-operative complication rates. By deflating the band, the restrictive mechanism can be easily reverted, which can be useful in some clinical conditions (e.g., pregnancy). It also promotes an effective and persistent result—up to 48 % excess weight loss after 12 years making it one of the most popular surgical options recently [75].

However, the long-term follow-up consists of frequent band readjustment and possible surgical revisions. More common complications include band erosion, band slippage, pouch dilation, port or tub disconnection and incisional hernia. Almost 50 % of patients will need a revision or removal of the band in the long run.

In addition, the restrictive intake of nutrients promotes food intolerance represented mainly by vomiting and can be more problematic and persistent than with other procedures, generating additional psychological and nutritional issues requiring regular follow-up from a multidisciplinary team [76].



**Fig. 41.2** Vertical sleeve gastrectomy: a partial gastrectomy is created by removing the great curvature including the fundus area. The tubular stomach creates a restrictive mechanism that is combined with the lack of ghrelin due to the fundus removal

*Vertical sleeve gastrectomy (VSG)*

VSG is a partial gastrectomy removing 80 % of the stomach, including the fundus and greater curvature, creating a 100–150 ml stomach (Fig. 41.2). VSG was first described in 1998 as the first step of the biliopancreatic diversion with duodenal switch procedure in super-obese patients ( $\text{BMI} > 50 \text{ kg/m}^2$ ) and since then it has been gaining popularity for all degrees of obesity.

Originally interpreted as an exclusive restrictive procedure, it has been shown that once the fundus cells are excluded there is a significant decrease in ghrelin secretion. Moreover the partial gastrectomy also interferes with gastric motility contributing to weight loss [74, 76].

As a single-stage intervention VSG offers less surgical risks and postsurgical complications. Recent data suggests an overall complication rate of 24 % and a mortality rate of 0.37 % [77]. It also promotes an excess weight loss of 57.7 and 60.6 % in 1 and 3 years respectively, better than the LAGB. The benefits have been attributed to the hunger control caused by the decreased levels of ghrelin that result from this procedure [78].

However, as it is a relatively recent procedure, long term data is still lacking, but it appears as an option for those with severe obesity or great risk of malnutrition.

#### *Intragastric balloon*

A temporary restrictive method consisting of a soft saline balloon placed via endoscopy in the stomach, causing a sensation of satiety and also occupying part of the area destined for nutrients. There are balloons of different volumes, from 500 to 600 ml.

It is an unapproved method worldwide, but a good option for a less invasive approach that can serve as an early step to weight loss. Data indicates loss that can reach as high as 48 % of excess weight. However it is a transient procedure, as the stomach can dilate and the weight is regained after a while [79].

The major complications described with these procedures are food intolerance, with consequent vomiting, nausea and some abdominal pain. Balloon migration and ulcers are also problems. Rarely some complications exist with the placement of the device [80].

#### *Biliopancreatic diversion (BPD)*

The original malabsorptive technique (Scopinaro) consists of a partial gastrectomy along with a gastroileostomy with a short common channel and a long Y-Roux limb promoting great malabsorption because of the short surface area of small intestine that will be in contact with the biliopancreatic secretion. Therefore, it is currently limited to special cases or revisional procedures because of the high rates of protein malnutrition, anemia, diarrhea, and nutritional deficiency of different components [76].

#### *Duodenal switch (DS)*

Combining restrictive and malabsorptive components, DS is a modified version of BPD created to minimize some of the nutritional

complications of the first technique. A sleeve or vertical gastrectomy (restrictive component) preserving the pylorus and the first part of the duodenum is accomplished along with a duodeno-distal small bowel anastomosis combined with a biliopancreatic limb creating a common channel of at least 100 cm in length, which is sufficient to minimize the malabsorptive component.

Several reports show a relevant loss of excess weight, up to 75 % on 10 year follow-up accompanied by highly effective control of hypertension, dyslipidemia, type 2 diabetes and sleep apnea. Compared to the BPD the weight loss and the metabolic improvements are sustained and have less nutritional complications [75, 81].

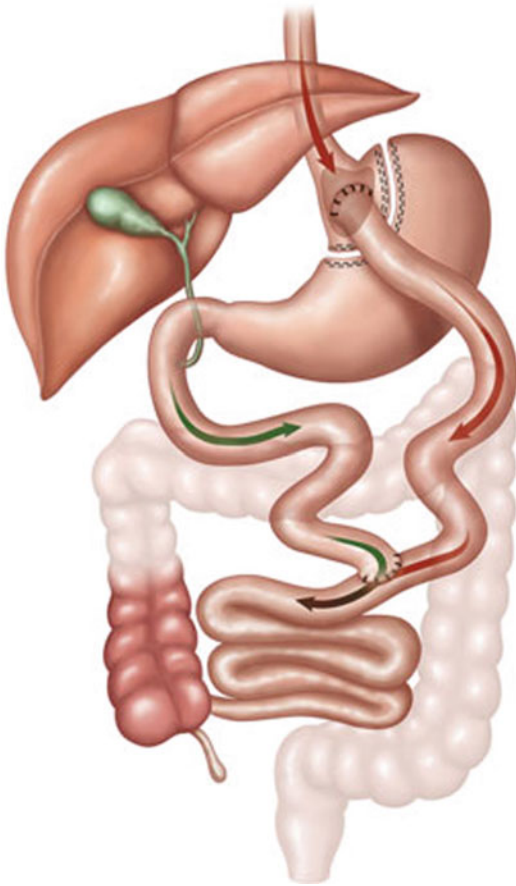
Even with the modifications promoted by DS technique the extensive malabsorptive component is still present creating important nutritional deficiency (such as protein, vitamin B12, and iron deficiency) and steatorrhea. It also induces more stomach ulcers, gastroesophageal reflux symptoms and has a greater risk of weight regain [82].

#### *Roux-en-Y gastric bypass (RYGB)*

RYCB is a combined restrictive and malabsorptive surgery that creates a small gastric pouch of 15–30 ml with an anastomosis to a Roux limb that bypasses 75–150 cm of the small intestine, connecting the pouch created with the proximal part of the jejunum and then to the ileum accompanied by a biliopancreatic limb. When both limbs are connected the common channel is created (Fig. 41.3).

The RYGB is the most common weight loss procedure in the USA [83], promoting an important loss of excess weight, reduction of clinical complications of obesity such as hypertension and generating an impact on glucose and lipid homeostasis that appears to be greater than with VSG [84].

However the malabsorptive mechanism can create a clinical complication known as dumping syndrome which occurs in up to 50 % of the patients and can be divided into early and late dumping which both interfere directly with quality of life, food intolerance, and consequently weight loss.



**Fig. 41.3** Roux-en-Y gastric bypass: the gastric pouch (15–30 ml) is connected to the proximal part of the jejunum creating part of the “alimentary limb.” The stomach reminiscent along with the duodenum generating the “biliopancreatic limb.” The alimentary and biliopancreatic limb are then connected 75–150 cm distally of the gastrojejunostomy creating the “common limb”

The complexity of the procedure and the greater number of anastomosis are also responsible for other relatively frequent acute and late complications such as stenosis, incisional hernia (mainly in open surgery), bowel obstruction, gastrointestinal leak, and marginal ulcers.

## Conclusion

Obesity is a very complex and heterogeneous disease, with serious health consequences which are often underdiagnosed and undertreated in clinical practice. It is of extreme importance that

physicians be more prepared to discuss obesity with their patients and less reluctant to perceive the condition as a chronic and dangerous disease that deserves a chronic and specialized medical management.

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# Bariatric Surgery in Treatment of the Obese Patient with Type 2 Diabetes

42

Manpreet S. Mundi and Maria Collazo-Clavell

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## Key Points to be Discussed

- Health risks of obesity
- Outcomes of medical nutrition therapy in patients with Type 2 DM
- Role of medications in the treatment of obesity
- Impact of bariatric surgery on Type 2 diabetes mellitus

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## Health Risks of Obesity

Major studies have clearly correlated obesity with the development of chronic metabolic conditions such as type 2 diabetes, hypertension, and hyperlipidemia [1, 2]. One of these landmark trials was the Nurses' Health Study, which began in 1976 when 121,700 female nurses 30–55 years of age began receiving and responding to questionnaires regarding medical, lifestyle, and other health-related information [1]. These women were then followed until 1996 with biannual questionnaires requesting updated information and identification of newly diagnosed diseases. Of the initial cohort, 84,941 female nurses were free of diagnosed cardiovascular disease,

diabetes, and cancer at baseline. This cohort was further analyzed for risk factors pertaining to the development of diabetes. During the follow-up period, 3,300 new cases of type 2 diabetes were documented with the most important risk factor being body mass index (BMI). The relative risk of diabetes was 38.8 in women with BMI of 35.0 kg/m<sup>2</sup> or higher, and 20.1 for women with BMI between 30.0 and 34.9 kg/m<sup>2</sup> when compared to women with BMI of less than 23.0 kg/m<sup>2</sup>. In fact, the relative risk was not only increased in the obese women but in the overweight groups as well. Women with a BMI between 25.0 and 29.9 kg/m<sup>2</sup> had a relative risk of 7.59 and 61 % of the cases of diabetes could be attributed to this overweight category.

Similar results were found in the third National Health and Nutrition Examination survey [2] (NHANES). NHANES included a home interview and a standardized physical exam to gather body weight and height. The results however, were similar in that the prevalence of type 2 diabetes increased dramatically with an increase in BMI. The prevalence of diabetes was 2.5 times higher in overweight men (BMI 25–29.9 kg/m<sup>2</sup>) and 3 times higher in overweight women when compared to normal weight group. This prevalence continued to increase and was 6 times higher in men and 5.5 times higher in women with BMI between 35 and 39.9 kg/m<sup>2</sup> when compared to normal weight group.

Of particular concern is that individuals with BMI ≥ 40 kg/m<sup>2</sup> (Class III obesity) are the most rapidly growing subset within the obese

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population. In fact, we have recently seen a 50 % increase in individuals with BMI > 40 kg/m<sup>2</sup> and a 75 % increase in the prevalence of individuals with a BMI > 50 kg/m<sup>2</sup> [3]. Unfortunately not only does obesity increase the prevalence of diabetes, it also makes it more difficult to treat by further increasing insulin resistance and glucose intolerance as well as exacerbating other metabolic complications such as hypertension and dyslipidemia [1, 2, 4–6]. Campbell et al. investigated the relationship of insulin sensitivity to body mass index (BMI) in 49 healthy volunteers who ranged between 80 and 240 % of ideal body weight [7]. By performing glucose clamp studies using various insulin concentrations, they found that insulin sensitivity for glucose disposal was impaired in individuals who were at least 20 % above ideal body weight for their height (BMI > 26 kg/m<sup>2</sup>). Beyond this threshold, insulin sensitivity and BMI were highly correlated ( $r = -0.8$   $p < 0.001$ ) in a linear fashion and accounted for 64 % of the variability in insulin sensitivity.

The combination of obesity with diabetes also proves to be a much dire situation in terms of mortality. The presence of excess body fat, particularly abdominal fat, along with the presence of insulin resistance leads to a pro-atherogenic lipid profile with high triglyceride and apolipoprotein B concentrations, an increased proportion of small dense LDL particles, and a reduced concentration of HDL cholesterol. This along with a pro-thrombotic and a pro-inflammatory profile significantly worsens an individual's risk of cardiovascular disease and overall mortality [8]. In fact, compared with normal weight individuals with diabetes, the mortality rate is 2.5–3.3 times higher in diabetics with body weights that are 20–30 % above their ideal weight and 5.2–7.9 times higher in those with body weights 40 % above ideal weight [9].

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### Treating the Obese Patient with Type 2 Diabetes

The exponential increase in the health risks of excess BMI and insulin resistance, make weight loss the first target in a patient with newly diagnosed type 2 diabetes. Calorie restriction and

weight loss have a positive effect on almost every risk factor associated with diabetes and obesity. There is a significant decrease in fasting glucose levels as noted in the UKPDS cohort who experienced weight loss in the first 3 months (a decrease from 205.2 ± 59.4 to 145.8 ± 32.4 mg/dL) [10]. This is accompanied by a decrease in fasting insulin levels [11], increase in insulin sensitivity [12], and improvement in beta-cell function [12]. Similar improvements are also noted in coexisting conditions such as hypertension and dyslipidemia. In the first few days of caloric restriction, a reduction in VLDL and triglyceride concentrations as well as increase in LDL particle size can be found [13]. With longer duration of therapy, a decrease in LDL concentration and an increase in HDL particles occur.

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### Lifestyle Modification

Despite the numerous benefits of weight loss in type 2 diabetes, it is often difficult for obese individuals to initially lose the desired weight and then maintain the weight loss. The Swedish Obese Subjects Study revealed that individuals placed on conventional diet and exercise had a 1.6 % increase in weight after 10 years [14]. Even when weight loss is achieved through aggressive lifestyle modification whether through medically supervised programs or commercial programs, weight regain commonly occurs once the intervention ends [15, 16]. Very low calorie diets (VLCDs) have been used to fill the gap between standard lifestyle modifications and bariatric surgery. The use of VLCDs grew rapidly in the 1970s with the introduction of the so-called liquid protein modified fast that provided 300–400 calories per day of liquid protein of low biological value obtained from collagen or gelatin hydrolysates. These diets tended to have inadequate micronutrient supplementation and resulted in a number of deaths secondary to arrhythmias [11]. Since then the composition of VLCDs has been changed to include high-quality protein supplemented with vitamins, minerals, trace elements, and essential fatty-acids with improved outcomes when used under direct medical supervision [17]. In fact, many studies have

reported typical weight loss of ~1–3 kg/week with higher results seen in the first 2 weeks due to fluid diuresis [17–19]. Weight loss with VLCDs is typically greater than with conventional diets and tends to occur more rapidly, producing faster and greater improvements in metabolic comorbidities. Henry et al. revealed a near normalizing of plasma glucose within 10 days of being placed on a VLCD in NIDDM subjects [20]. Unfortunately, this effect can be transient, as fasting plasma glucose values tend to rise once patients are taken off of the VLCD and gain weight. Recidivism or weight regain is seen in virtually all patients once VLCD is stopped. Less weight loss is noted with subsequent VLCD trials due to changes in metabolic rate, making VLCDs an unlikely long-term solution.

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## Medications

Pharmacological options have increased recently with the approval of two new agents with the indication of long-term use for weight loss. Orlistat, a lipase inhibitor, has been on the market for a number of years and has been shown to result in approximately 5.4–10.6 kg weight loss at 1 year with 46–73 % of patients achieving greater than 5 % and 20–41 % achieving greater than 10 % weight loss [21, 22]. Modest improvements in HbA1c have also been reported with one randomized placebo control study revealing a decrease of –0.74 % with Orlistat 120 mg tid versus –0.31 % in the placebo group [21]. A modest reduction in HbA1c was observed in patients despite minimal weight loss with Orlistat versus placebo (–0.29 % vs. +0.14 % respectively). Other studies have revealed an average HbA1c reduction of 0.28–1.1 % [22]. Meta-analysis by Johansson et al. [23] revealed a statistically significant improvement in hypertension with a reduction of 1.9 mmHg in systolic blood pressure and 1.5 mmHg for diastolic blood pressure. Compared with patients without diabetes, patients with diabetes experienced smaller and nonsignificant reductions of SBP and DBP.

Lorcaserin, a selective serotonin 2C receptor agonist, increases satiety and has been studied for weight loss in patients with type 2 diabetes in a

low dose (10 mg daily) and high dose (10 mg twice a day) formulation [24]. At 52 weeks, a 5 % weight loss was achieved by 37.5 % of high dose, 44.7 % of low dose, and 16.1 % of patients on placebo. A 10 % weight loss was achieved by 16.3 %, 18.1 %, and 4.4 %, respectively. Both treatment groups saw an average HbA1c reduction of close to 1 % with a decrease in fasting plasma glucose of approximately 25 mg/dL. Changes in cholesterol and triglycerides were small in all treatment groups, and the differences between treatment groups were not significant. Systolic and diastolic blood pressure also decreased from baseline in the lorcaserin BID and placebo groups, but there was no statistically significant difference between treatments.

Combination of phentermine and topiramate has also been approved for long term use for weight loss. It has been studied in a low-dose (PHEN/TPM CR 7.5 mg/46 mg) or high dose formulation (PHEN/TPM CR 15 mg/92 mg) for up to 2 years [25, 26]. At 108 weeks, the high dose group lost 10.5 % of body weight while the low dose group lost 9.3 % and the placebo group gained 1.8 % despite lifestyle interventions including behavioral therapy based on the LEARN manual. Both systolic and diastolic blood pressures were reduced by 3–5 mmHg from baseline. They also found a 54 % reduction in progression to type 2 diabetes in the low dose and a 76 % reduction in high dose groups. Although, less than 10 % of subjects enrolled in the trial had type 2 diabetes, the average HbA1c reduction was 0.4 % in the low dose and 0.2 % in the high dose when compared to no change in the placebo group. These medications do show some promise for use in patients with type 2 diabetes but long-term data is necessary. Patient attrition also continues to be an issue as greater than 50 % of patients enrolled, dropped out of the 2 year study of phentermine/topiramate.

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## Bariatric Surgery

Challenges with medical nutrition therapy and weight loss medications have made bariatric surgery a treatment alternative for long-term sustained weight loss. The popularity of bariatric surgery has grown since its inception in the

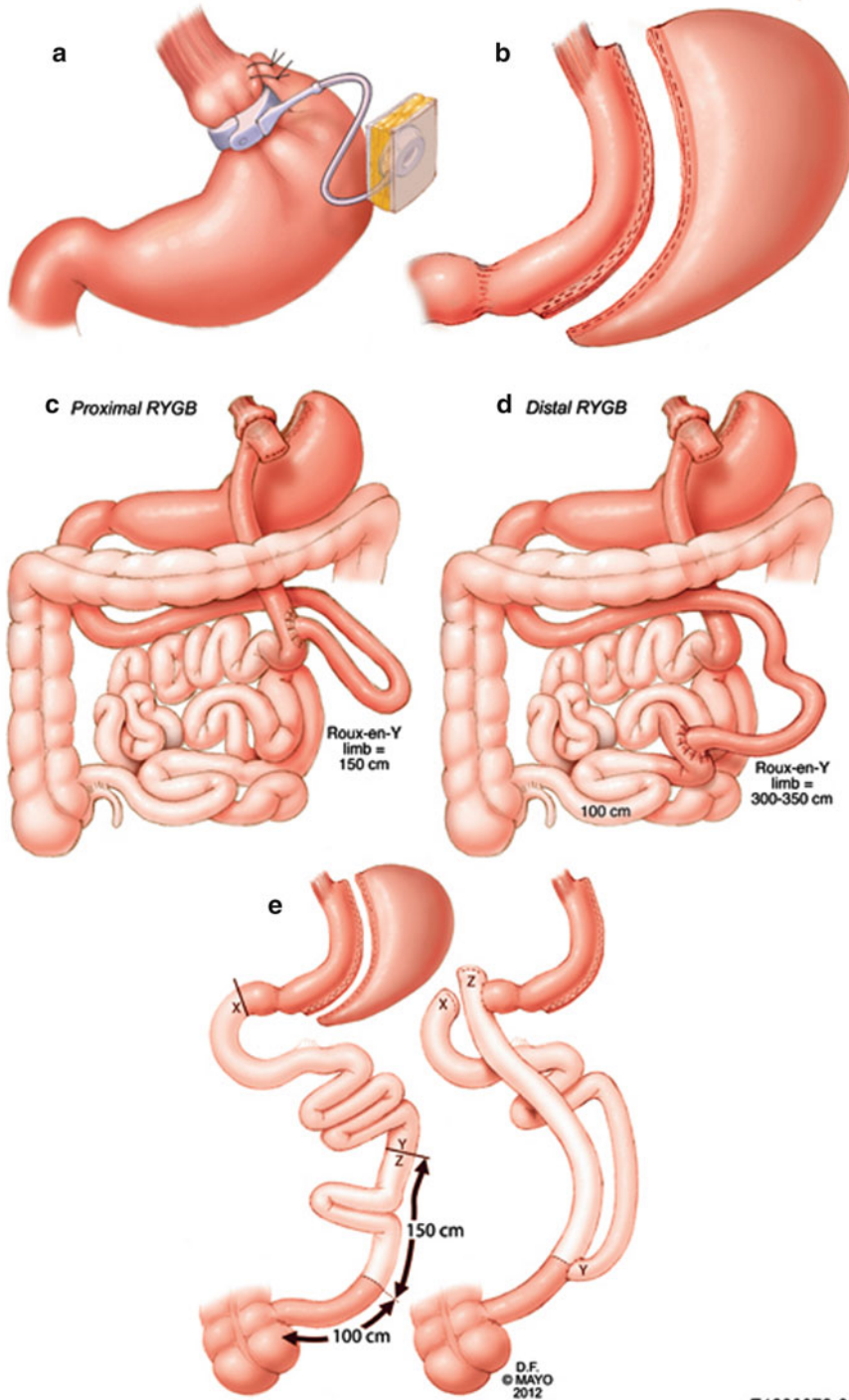
1950s [27]. Currently, the laparoscopic adjustable gastric banding (LAGB) and the gastric sleeve are the main restrictive procedures being offered. The LAGB is an implanted device that is placed around the proximal portion of the stomach and restricts flow of food (Fig. 42.1a). It does require routine adjustment after placement to ensure sufficient restriction while avoiding complete stenosis or laxity. The gastric sleeve is a restrictive procedure that until recently was being performed as part of the biliopancreatic diversion duodenal switch (BPD-DS) in a staged procedure in the superobese (Fig. 42.1b) [28]. It involves resection of the majority of the stomach along the greater curvature, decreasing gastric volume by over 90 %. The main mechanism of weight loss with these procedures is through a reduction in volume of food intake as well as early satiety.

Roux-En-Y gastric bypass (RYGB) is currently the most common bariatric operation performed in the United States (Fig. 42.1c, d). In this procedure, the stomach is partitioned into a much larger distal portion and small (~15 ml) proximal portion, which receives food from esophagus. The proximal portion is then joined with the jejunum restricting the volume of a typical meal dramatically. The distal portion of the stomach, duodenum, and early jejunum are then connected downstream of the gastrojejunal anastomosis, thus bypassing this portion of intestine from receiving pancreatic enzymes and bile. The length of this bypassed portion of the jejunum or Roux limb can range from 75 cm to 250 cm to produce the desired amount of weight loss. Biliopancreatic diversion (BPD) performed with or without the duodenal switch (BPD-DS) are the main malabsorptive procedures being offered (Fig. 42.1e). These procedures include partitioning of the stomach in the case of BPD or creation of gastric sleeve as seen in BPD-DS. Then an anastomosis is formed between the stomach and the jejunum (BPD) or duodenum and jejunum (BPD-DS). Malabsorption of nutrients is then created when the biliopancreatic limb is joined to the distal small intestine, allowing only a short segment of “common channel” where digestive enzymes from pancreas and bile mix with food.

## Impact of Bariatric Surgery on Type 2 Diabetes

Bariatric surgery is efficacious in producing weight loss. The Swedish Obese Subjects study compared outcome in 2010 patients who underwent bariatric surgery with a matched control group who received conventional treatment [14]. After 1–2 years, the RYGB group had lost 32 % of their body weight with the vertical banded gastroplasty (VBG) group losing 23 %, and the LAGB losing 20 % (Table 42.1). The conventional treatment group initially lost weight at 1 year but then regained by 2 years. After 10 years, the weight losses were 25 % for the RYGB, 17 % for VBG, and 15 % for LAGB. Although dropout was an issue, the long-term weight loss in the surgical group was considerably greater than conventional treatment group. A meta-analysis of 621 studies by Buchwald et al. revealed an average weight loss of 38.5 kg or 55.9 % of excess body weight loss for four distinct surgical procedures including BPD-DS [29]. The weight loss appeared to be sustained as studies with 2 or more years of follow-up revealed a mean total loss of 41.6 kg or 59 % of excess body weight loss. The results were more impressive in patients with diabetes with a mean total loss of 40.6 kg or 64.4 % of excess weight and loss of 42.9 kg or 58.0 % of excess weight in studies beyond 2 years.

Equally impressive improvements in weight related medical comorbidities have been reported with bariatric surgery. Pories et al. first reported on the impact of bariatric surgery (RYGB) on type 2 diabetes and noted that 82.9 % of patients with non-insulin dependent diabetes (NIDDM) and 98.7 % of patients with glucose impairment experienced euglycemia without medications [30]. They also noted that 353 of the 608 patients (58.1 %) had hypertension prior to surgery and this rate was reduced to 14 % afterwards. Buchwald et al. in a meta-analysis also noted similarly impressive resolution of diabetes in 78.1 % overall and an improvement or resolution in 86.6 % [29]. Diabetes resolution was greatest for patients undergoing BPD-DS (95.1 % resolution



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**Fig. 42.1** Illustration of main types of bariatric surgery currently being performed. *By permission of Mayo Foundation for Medical Education and Research. All rights reserved*

**Table 42.1** Percent weight loss with various interventions

	6 months	1 year	2 years	3 years	4 years	5 years	>5 years
Diet alone [49]	5.0	4.6	4.4		3.0		
Diet plus exercise [49]	8.5	4.0	4.0	4.0	4.0		
Meal replacements [49]	9.6	7.5					
VLCD [49]	16.0	10.0		5.0			
Orlistat [49]	8.0	8.0	7.0	7.0	5.3		
Lorcaserin 10 mg bid [24]	5.0	4.5					
Phen/top 15 mg/92 mg [26]	12.0	13.0	11.0				
LAGB [14]	18.0	21.0	20.0	18.0	17.0	16.0	15.0 (10 years)
VBG [14]	23.0	26.0	23.0	21.0	20.0	18.0	17.0 (10 years)
RYGB [14]	27.0	33.0	32.0	30.0	29.0	27.0	25.0 (10 years)

Note: percent weight loss provided from pertinent landmark studies. Data from gastric sleeve and BPD-DS not available in this format at the time of publication

rate) compared to 80.3 % with RYGB, and 56.7 % with LAGB. Hypertension resolved in 61.7 % of patients and resolved or improved in 78.5 % [31]. Obstructive sleep apnea was resolved in 85.7 % of patients and resolved or improved in 83.6 % [31]. Hyperlipidemia improved as well in greater than 70 % of patients [31]. Brethauer et al. conducted a similar meta-analysis for the gastric sleeve both as a staged and primary procedure [32]. They reported a weight loss of 60.4 % of excess weight in patients where gastric sleeve was the primary procedure and 46.9 % when it was used as a staged procedure. Seventy percent of patients with type 2 diabetes had an improvement or remission of their disease.

## Mechanisms of Improvement in Diabetes

In addition to the improvement in insulin resistance produced by weight loss alone, additional mechanisms have been proposed to explain improvement and/or resolution of DMT2 after bariatric surgery. Kellum et al. first demonstrated the impact of gastric bypass on gastrointestinal hormones reporting a dramatic increase in enteroglucagon response to meal not observed after vertical banded gastroplasty [33]. Enteroglucagon corresponds to the protein product of the glucagon gene in the gut that generates many gut hormones (incretins) such as glucagon-like peptide 1 (GLP-1) and 2 (GLP-2), glucagon, glicentin, and oxyntomodulin [34]. Additional studies revealed

that glucose-stimulated incretin levels increase after gastric bypass when they are typically blunted in T2DM [35–37]. Laferrère et al. revealed that this incretin effect can result in an increase in insulin secretion to levels seen in matched controls without T2DM only 1 month after gastric bypass [37]. This effect does not appear to be due to weight loss alone as shown in a study by Laferrère et al. that compared the change in incretin levels in obese women with T2DM undergoing RYGB versus their matched controls who lost an equivalent amount of weight with diet [38]. They found that GLP-1 levels after oral glucose increased sixfold after surgery, but not after diet. In fact, after diet induced weight loss, the levels of GLP-1 and GIP tended to decrease.

Additional beneficial changes in incretin secretion have been reported after bariatric surgery resulting in both central (hypothalamic appetite regulation) and peripheral (ileal break and delayed transport of nutrients through the gastrointestinal tract) mechanisms. Obese individuals typically have decreased basal and postprandial PYY [39] as well as decreased postprandial GLP-1 response [40], leading to lower feelings of satiety. This trend can be worsened with diet-induced weight loss as Sumithran et al. [41] revealed an increase in ghrelin and a reduction in peptide YY (PYY), amylin, and CCK leading to an increase in ratings of hunger, desire and urge to eat, as well as prospective consumption. The opposite has been reported after bariatric surgery [42–44]. One of the proposed mechanisms after gastric bypass is



the increased delivery of unabsorbed nutrients to the GLP-1 and PYY producing L-Cells in the distal small bowel, resulting in amplified secretion of the incretins [45]. Others have speculated that there is a change in macronutrient composition after surgery that may result in alteration of incretin secretion. Evans et al. [45] investigated the mechanism of this change by comparing subjects who underwent RYGB with matched controls who were given a hypocaloric diet similar to a typical post-RYGB diet for 7 days. They provided the groups with a high protein or high fat meal. Gastric bypass resulted in augmented postprandial GLP-1 and PYY response to both meals. No augmentation in GLP-1 and minimal augmentation in PYY were seen in the low-calorie diet group. There was also a dramatic increase in hunger ratings in the diet group both before and after meal when compared to the RYGB group.

In addition to augmentation of GLP-1 and PYY secretion, bariatric surgery has also been noted to result in a change in ghrelin levels, a neuropeptide synthesized mainly in the antrum of the stomach that is known to have an orexigenic hypothalamic effect. Cummings et al. compared ghrelin levels before and after both a 6-month dietary program as well as gastric bypass [42]. They noted a significant rise in ghrelin levels in the dietary weight loss group. On the other hand, the gastric bypass subjects had markedly lower ghrelin levels compared to both the lean and obese controls, despite weight loss. They also did not have an oscillation in levels in relation to meals, an effect felt to be due to the process of over-ride inhibition that occurs when the stomach and duodenum are isolated from food. This tends to support patient subjective improvements in hunger and appetite regulation as exogenous ghrelin has been shown to increase subjective hunger, food intake, as well as decrease catabolism of fat and metabolic rate, leading to increase in body weight.

These positive changes in incretin secretion are not only isolated to RYGB and have also been noted in patients undergoing gastric sleeve. Langer et al. prospectively compared ghrelin levels after gastric sleeve and LAGB and noted that they were dramatically reduced after the gastric sleeve and yet increased following LAGB. Peterli et al. [46] compared the change in ghrelin levels

after a RYGB and gastric sleeve and observed a decrease in ghrelin levels within a few weeks of either procedure. The decrease was more prominent in the gastric sleeve group when compared to the RYGB group, a finding that can be explained by the fact that ghrelin producing cells are being removed in the gastric sleeve versus being isolated from nutrients in the RYGB. Gastric sleeve patients also had an improvement in GLP-1 response to meals that was less prominent than the RYGB group. This is a startling finding given the fact that the foregut is not being bypassed. One explanation for increased GLP-1 release may be that there is an additional trigger such as CCK for release of GLP-1 in addition to nutrient stimulation of L-cells. It also seems that despite the lack of bypass in gastric sleeve, accelerated gastric emptying and earlier contact of chyme with L cells may still be occurring. Scintigraphic studies have shown accelerated gastric emptying for solid and liquid foods up to 2 years after sleeve gastrectomy [47].

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## Future Therapies

There is ongoing investigation of novel therapies targeting the obesity epidemic and its associated medical comorbidities. New medications, new “metabolic” operations aimed at improving the mechanisms contributing to insulin resistance and new procedures such as the Endo barrier hold promise as additional tools in the treatment of obesity and Type 2 diabetes.

Aguirre et al. showed that weight loss occurs with endo-barrier and there was a significant reduction in oral intake (~27 fewer kcal/day) in these mouse models resulting in a 20 % reduction in body weight [48].

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## Summary

The rise in the prevalence of obesity is a recognized contributor to the rising incidence of Type 2 diabetes. Despite the reported benefits of weight loss through lifestyle changes, achieving significant and sustained weight loss remains a challenging prescription for most patients.

Bariatric surgery has been shown to be an effective therapeutic alternative in the management of the patient with obesity. Yet, it is the impact of bariatric surgery on weight related comorbidities, particularly Type 2 diabetes that has led to a dramatic rise in the number of operations performed. Being well informed regarding the bariatric operations currently offered and their impact on Type 2 diabetes is critically important as we assess the potential role of these operations in the management of our patients.

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