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Health and Treatment Strategies in Obesity

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Preface

The explosion of obesity with its multiple comorbidities and devastating effects on all aspects of an individual's life has brought it to our attention. The increasing number of adolescents affected by obesity as well as the 'global' surge of obesity has led to greater interest and newer more effective treatments. The developed countries have a greater prevalence of obesity. While our genetic pool seems to have remained relatively the same over the ages, our environment has changed rapidly. We seem to be consuming more foods that are high in caloric value, while our energy expenditure has lessened by the use of machines that reduce the intensity of labor. The increasing prevalence of obesity in the USA and its medical, social, psychological and economic implications has made it a national health crisis. Obesity has been predicted to be the number one health problem globally by the year 2025 with the USA leading the way. Obesity is thought to be overtaking cigarette smoking to soon become the leading cause of death in the USA.

When compared to other serious health issues like HIV and lung cancer, the funding for obesity research does not match the threat it poses. However, great strides have been made in recent years to discover the cause of obesity as well as successful treatments for it. The discovery of neuropeptides as well as hormones regulating energy metabolism have led to a better understanding of the development of obesity. This has helped open doors to procure possible treatments, the end result hoped for being a medication that affects energy metabolism with effective and long-term weight loss without dangerous side effects. While the perfect drug to cure obesity has eluded us just yet, it does seem to be around the corner. Currently, the most effective treatment for obesity and its comorbidities in selected patients is bariatric surgery.

This volume reviews the strides we have made in our understanding of obesity with a special focus on bariatric surgery. Several nutritional strategies and diets are discussed, with a special section on dietary changes after bariatric surgery.

We have reviewed the most current understanding of the pathophysiology of energy metabolism. While bariatric surgery does produce long-lasting results, patient selection is important, as postoperative compliance is essential for a successful outcome. The prevalence of psychiatric illness in the obese is similar to those with normal weight; however, obese patients seeking treatment have an increased prevalence of psychiatric illness, most commonly major depression. Psychiatric illness is not a contraindication for bariatric surgery; however, it is important that the patient be mentally stable and engaged in treatment to ensure postoperative compliance and optimal outcome. Body image and sexual functioning are closely intertwined with obesity. Due to the rapid weight loss which occurs after bariatric surgery, these aspects need to be assessed pre- and postoperatively to ensure that the patient receives appropriate help to optimize the surgical outcome. Body contouring surgery is helpful in bariatric surgery patients that have massive weight loss. This helps patients improve mobility as well as body image self-esteem as discussed in the chapter by Rajiv Y. Chandawarkar. Binge eating disorder is being recognized as a frequent comorbid condition in the obese. While these patients are effectively treated in the initial 18 months after bariatric surgery, they become 'grazers' a year and a half after the surgery and can regain their weight. This volume deals specifically with cognitive behavioral therapy and interpersonal therapy for binge eating disorder that help sustain the benefits of bariatric surgery over a longer term and give the patient alternate coping skills.

The manifold effects that bariatric surgery has on the patient's health, physical as well as psychological, make it the most effective treatment of obesity and its infiltrative effects on all aspects of the patient's life. Until we discover the 'perfect pill' to overcome morbid obesity, bariatric surgery seems to be the most effective treatment in selected patients.

Varsha Vaidya

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Recent Advances in Obesity: Adiposity Signaling and Fat Metabolism in Energy Homeostasis

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Abstract

Interactions between our conserved 'thrifty genotype' and current trends toward reduced physical activity and increased food intake are posited as the root cause of the rising prevalence of obesity in the modern era. The past decade has seen tremendous advances in our understanding of the physiological regulation of energy balance and adiposity, and important insights into the pathogenesis of obesity. We have gained a more comprehensive view of the energy homeostasis system from the discovery of the adiposity hormone leptin, the subsequent identification of hypothalamic and other brain neuropeptide systems controlling energy balance, and the progress in understanding the molecular mechanisms by which cells can sense and respond to changes in metabolic state. Numerous targets have been identified for potential pharmacological and genetic approaches to obesity management. Some of the most recent developments are prototypic compounds that manipulate fat metabolism, both in peripheral tissues and in the brain, to reduce body fat synthesis and storage and to increase fat oxidation, to reduce food intake, and to increase energy expenditure.

Obesity is now the most common metabolic disease in affluent nations. In the United States 65% of adults are overweight, and 31% are obese with a body mass index (BMI) of 30 or greater. Among children and adolescents, 31% are at risk for overweight and 16% are overweight [1]. The increased prevalence of obesity is appreciated to result from an interplay between our evolutionarily conserved 'thrifty genotype' [2] and the combination of our current intakes of high-calorie foods with an increasingly sedentary lifestyle [3]. Populations of other developing nations are shifting toward Western-like diet and inactivity, and the 'obesity epidemic' is becoming a pandemic. This does not bode well for world health. The health risks associated with obesity are now estimated to

exceed those associated with smoking, alcoholism, and poverty in the United States [4]. These risks include a staggering array of metabolic, cardiovascular, respiratory, gastrointestinal, urogenital, musculoskeletal, neurologic, and psychological complications [5].

Fortunately, the past decade has seen rapid expansion of our understanding of the biochemical events thought to produce obesity. The advances have largely come from the fields of molecular biology and genetics. The discoveries of the ob gene product leptin [6], its receptors [7], and its role as an adiposity signal to control food intake [8] proved most consequential for the subsequent demonstration of circuits in the brain that regulate energy balance [9–15]. This has been perhaps the most fertile ground for identifying targets for pharmacological approaches to the treatment of obesity. However, other recent developments in our understanding of energy sensing from both a central nervous system and a peripheral tissue standpoint, as well as in fat metabolism and fat cell physiology, may provide additional inroads to future antiobesity strategies.

Obesity research has become quite broad in scope, and at the same time increasingly detailed at the mechanistic level. This review will cover basic issues of and systems involved in energy homeostasis, emphasizing systems related to adiposity and fat metabolism. It will provide a brief overview of important results from basic science that have already shown relevance to human obesity, and identify recent discoveries and paradigm shifts that we think are guiding obesity research today. Finally, it will highlight the potential clinical relevance of some of the latest and most promising data from animal and cell models.

Energy Homeostasis in the Context of Evolution and Gene-Environment Interactions

The term homeostasis refers to the maintenance of the internal environment within narrow and rigidly controlled limits, in a manner that ensures survival of the organism in the face of challenges from the external environment. Major functions important in homeostasis are fluid and electrolyte balance, acid-base regulation, thermoregulation, and metabolic controls. Cellular energy, in the form of high-energy molecules such as ATP, is required to drive key steps for these and other physiological processes. Acquisition of food to provide this energy, and maintenance of adequate energy stores to be utilized when food is scarce, are thus fundamental for survival.

It has been asserted that 95% of human biology was naturally selected under the environmental pressures of the Late-Paleolithic era, 50,000–10,000 BC [16], when humans existed as hunter-gatherers. Food was usually not available on a regular basis. People were more likely to survive and pass on their genes if they

had what Neel [2] called a 'thrifty genotype' that encoded for making an individual 'exceptionally efficient in the intake and/or utilization of food'. This translates into strong appetitive drive, efficient storage of fuels in the body when food is available, and efficient mobilization of the stored energy during times when food is scarce or when physical exertion is required. Energy intake and energy expenditure were inextricably linked, because physical effort was required to acquire food [17]. The Stone-Age lifestyle was punctuated by cycles of feast and famine, and of exercise and rest, and it is posited that these were linked to the selection of genes that, in that environment, were likely to result in survival [3].

These conserved traits have new implications for human health and survival in the modern era. With the rapid development of agriculture and industry, many humans now have ready access to food. The food is more often highly palatable, thus more likely to be consumed in large quantities [18]. Furthermore, many individuals no longer need exert significant energy to acquire food, and daily life requires considerably less incidental exercise. It is now argued that the 'thrifty genotype' [2], geared to defend against weight-loss rather than weight-gain [10, 19, 20], is at odds with modern life, and that this is the root cause of the rising prevalence of obesity worldwide [21].

If body weight and adiposity are to remain stable, the body must be in energy balance, with energy intake equal to energy expenditure. If energy balance is not maintained, then fat and body weight will be lost, or gained, over time. In developed regions of the world, many people are clearly in positive energy balance. If the objective is to lose weight, then energy intake must be reduced, energy expenditure must be increased, or both must occur. From a prevention standpoint, obesity may be avoided by measures to defend energy balance. These goals are sometimes achievable through moderation of calorie intake and/or increased exercise. In other cases, rare monogenic mutations, or more common polygenic etiologies, can result in behavioral and metabolic disturbances that stand in the way of energy balance. Thus, for some people lifestyle changes may not be enough to achieve healthy adiposity levels and body weight. In these cases, pharmaceutical or even surgical approaches may be warranted.

The Energy Homeostasis System

Any homeostatic system consists of an afferent limb, an integrator, and efferent limb, and the regulated variable. We have come to understand that components of the energy homeostatic system include: (1) *afferent signals* categorized as either adiposity signals or meal-related signals; (2) the brain, particularly the hypothalamus and hindbrain, as a *central integrator* of afferent signals; (3) *efferent limbs*, such as neuronal pathways, neuropeptides, neurotransmitters, and hormones that adjust levels and types of food intake, energy expenditure, and

metabolic fluxes, and (4) the *regulated variable(s)*, in this case the *functioning* of a system that ingests, digests, stores, utilizes, and eliminates energy. This system includes the gastrointestinal tract, depots of adipose tissue, the liver, and muscle.

Afferent Signals to the Central Integrator

The sensory signals are categorized as (1) meal-related signals, which are short acting and reflect the amounts and distributions of calories and macronutrients in the gastrointestinal tract, and (2) adiposity signals, upon which meal-related signals are superimposed. Adiposity signals are long acting, and reflect the fat mass of the body. Although both categories regulate energy balance, in part by interacting, it is currently thought that the longer-term adiposity signals are the major players in the regulation of body weight.

When animals are fasted they rapidly lose weight, initially as fat. Upon renewed access to food, they initially ingest more calories than usual, resulting in recovery of the lost fat and weight. As body weight approaches normal levels, there is a gradual return to normal levels of energy intake. Based on these phenomena, Kennedy [22] hypothesized that inhibitory signals are generated in proportion to the fat mass and act on the brain to tonically suppress food intake. Such adiposity signals have since been identified as hormones that circulate in the blood in concentrations that are proportional to the body's fat mass.

Before the influx of modern genetic and molecular biological approaches to the field of obesity research, insulin had been identified as a strong candidate adiposity signal [23]. However, because the discoveries in the mid-1990s of the ob gene product leptin [6] as an adiposity signal proved most consequential for subsequent demonstrations of circuits in the brain that regulate energy balance [9–15], we will focus on leptin and the attendant discoveries. The experimental data suggest a number of strategies by which the mechanisms of action of leptin and other potential adiposity factors might be manipulated in the clinical setting to prevent or treat obesity.

Leptin as an Adiposity Signal

Over the last 100 years, only five single-gene alleles occurring as spontaneous mutations have been identified in modern inbred strains of rodents: Ay, db (in mice, or fa in rats), fat, ob, and tub [24]. Significantly, three of these, Ay, db, and ob are in some way related to the adiposity signal leptin. Leptin was discovered by positional cloning of the obese gene, ob [6]. Leptin is produced and secreted by white adipocytes [6], circulates in the plasma at levels proportional to the fat mass [25], and enters the central nervous system in proportion to its levels in plasma [26]. The leptin receptor, like leptin, was discovered

through positional cloning [7] of the diabetes gene, db. Leptin receptors are expressed by neurons in the hypothalamus that are important for the control of food intake and energy balance [27–29].

In three studies published in the same 1995 issue of *Science*, recombinant murine [8, 30, 31] and human leptin [30] were administered systemically by intraperitoneal injection (i.p.) into mice homozygous or heterozygous for mutated ob gene [31], ob/ob and db/db mice [8], and ob/ob, db/db, and dietary-induced obese (DIO) mice [30]. With the exception of the db/db mice lacking the leptin receptor, mice reduced their food intake and lost weight in response to acute and chronic administrations of leptin. Consistent with the notion that leptin is an adiposity signal to the brain, leptin administered intracerebroventricularly (i.c.v.) reduced food intake and body weight in ob/ob mice deficient in leptin, but not db/db mice lacking the receptor [30]. In mice that are homozygous [32] or heterozygous [33] for the db mutation, selective overexpression of the leptin receptor in neurons amends the disruptions in endocrinology, metabolism, and feeding behavior to reverse the obesity.

Leptin-Related Mutations in Murine and Human Obesity

Because obese mice with single-gene mutations had long been the subjects of metabolic and endocrinological experiments, the positional cloning of ob and db lent to rapid insight into the biology underlying these mutations [24]. Both ob/ob and db/db mice exhibit early defects in thermogenesis [34], increased fat mass by the age of 2 weeks, and hyperphagia and obesity by age of weaning at 21 days [35, 36]. Administration of leptin to ob/ob mice corrects their low basal body temperature, low levels of oxygen consumption (VO_2), and hypoactivity [31], and decreases body weight by decreasing fat mass and percentage of body fat, without affecting lean mass [8, 31]. Leptin- and leptin receptor-deficient mice both have marked activation of the hypothalamic-pituitary-adrenal stress axis that results in high plasma levels of corticosterone, the active glucocorticoid in rodents, which is thought to contribute to the obese and diabetic phenotype [37, 38]. Depending on other genetic influences [39], they also fail to enter puberty due to hypogonadotropic hypogonadism.

The discoveries of leptin and leptin-receptor mutations in mice have permitted the identification of similar rare single-gene mutations in humans. Two families with congenital leptin deficiency have been reported [40, 41]. Each family has a different kind of homozygous ob mutation, but they exhibit similar phenotypes of hyperphagia, morbid obesity, and hypogonadotropic hypogonadism. In addition, a mutation of the leptin-receptor, resulting in a truncated receptor with no transmembrane or intracellular domain, has been reported in one family [42]. Unlike the ob/ob and db/db mice, leptin- and leptin-receptor deficient human patients do not seem to have reduced energy expenditure or increased

efficiency for fuel storage. Hyperphagia appears to be the dominant contributor to these human obese phenotypes [43]. Also, unlike the mouse models, these human patients do not exhibit hyperactive HPA axes or elevations in circulating cortisol [43]. Like leptin-deficient mice, patients with defective leptin receptors have a phenotype of hyperphagia, morbid obesity, and failure to initiate puberty, but with additional outcomes of growth retardation and hypothyroidism. As predicted in studies of ob/ob mice [8, 30, 31], human patients that lack leptin but have functional leptin receptors respond well to long-term therapy with subcutaneous leptin injections. Treating obese patients that have congenital leptin deficiency with leptin substantially normalizes their appetite, fat mass, hyperinsulinemia and hyperleptinemia, and hypothyroidism [43–45], and permits initiation of puberty in pediatric patients [43, 44].

Interestingly, some relatives of patients with congenital leptin deficiency are heterozygous for the mutation, have lower levels of leptin than normal, and are moderately obese [46]. These heterozygotes may be similar to a minority subset of common obesity, without known mutations of leptin signaling, in whom plasma levels of leptin that are lower than normal predict obesity [47]. The possibility that individuals with low levels of leptin are treatable with systemic administration of leptin has not yet been explored.

Leptin Signal to the Central Nervous System

In the more typical situation of common obesity (not defined by known mutations), serum leptin levels are higher than normal, in proportion to the increased fat mass [25]. The increased adiposity despite high levels of the negative-feedback adiposity signal leptin suggests a state of leptin resistance in common obesity. Indeed, a clinical trial using chronic subcutaneous leptin in obese patients yielded variable results [48]. It has been hypothesized that leptin resistance is due to decreased leptin signaling in the brain. Factors which may contribute to leptin resistance are (1) diminished transport of leptin into the central nervous system; (2) defective intracellular signaling downstream of leptin receptor in key hypothalamic nuclei, and (3) defects in the activity of neuropeptide and neurotransmitter systems in the central nervous system, downstream of leptin-receptive neurons.

The notion that leptin resistance may result from defective transport of leptin across the blood-brain barrier is suggested by the finding that, in DIO mice, leptin has diminished potency when given systemically, but normal potency when administered directly into the brain [49]. Of the six leptin receptor isoforms, the predominant ‘short receptor’ (Ob-Ra) is widely expressed in multiple tissues including the choroid plexus and brain microvasculature [50]. In mice, Ob-Ra in brain microvessels appears to contribute to leptin transport into the central nervous system [51]. The mechanisms by which leptin transport is

reduced during obesity are not yet identified, but a recent study has shown that intravenous triglycerides, but not fatty acids, produce an immediate and long-lasting reduction in leptin transport into the central nervous system [52]. The high plasma levels of triglycerides in obese patients may therefore interfere with normal adiposity signaling feedback to the brain, exacerbating the obesity.

The leptin receptor isoforms have similar extracellular ligand-binding and transmembrane domains, but only the 'long receptor' (Ob-Rb) has intracellular components necessary for activation of the Janus-activated kinase-2 (JAK2) and signal transducer and activator of transcription-3 (STAT3). Ob-Rb is plentiful in nuclei of the hypothalamus that are important in the regulation of energy balance, particularly the arcuate (ARC), paraventricular and dorsomedial hypothalamic nuclei (PVN, DMH), and the lateral hypothalamic area (LH) [53]. JAK-STAT signaling in these nuclei results in the transcription of genes. Among these is suppressor of cytokine signaling-3 (SOCS3) [54, 55], that inhibits further leptin signal transduction. Peripheral leptin administration to ob/ob, but not db/db mice, rapidly induces SOCS-3 mRNA in areas of hypothalamus expressing high levels of Ob-Rb [56]. Expression of SOCS-3 mRNA in the ARC and DMH is increased in Ay/a mice, a model of leptin-resistant murine obesity [56]. The potential contribution of SOCS3 to acquired forms of leptin resistance and obesity is an active area of study. Another molecule, protein tyrosine phosphatase 1B (PTP1B), has been implicated as a negative modulator of leptin signaling through JAK-STAT [57–59]. PTP1B is expressed in hypothalamic neurons that have Ob-Rb, and dephosphorylates JAK2 [57, 59]. PTP1B-knock-out mice are hypersensitive to the hypophagic and weight-loss effects of peripheral leptin administration [57, 59]. Furthermore, leptin-deficient ob/ob mice that also lack PTP1B exhibit an attenuated weight gain, a decrease in adipose tissue, and an increase in resting metabolic rate [57]. Thus, molecules such as SOCS3 and PTP1B that modulate leptin signaling are attractive targets for antiobesity therapies. In addition to the JAK-STAT pathway, leptin-activated Ob-Rb regulates intracellular signals that are also downstream of insulin receptors, including PI3-kinase [60], as well as MAP-kinase, ERK, Akt, AMPK, and IRS-1 [61]. These molecules and their intracellular signaling pathways may provide other options for antiobesity therapies.

Hypothalamus as Central Integrator

Arcuate Nucleus and Neuropeptide Systems for Regulation of Energy Balance

The identification of leptin and its sites of action in the hypothalamus led to rapid advances in our understanding of CNS neuropeptide systems that

regulate energy homeostasis in response to circulating signals such as leptin that vary with metabolic state. The arcuate nucleus (ARC) is a critical hypothalamic site for the regulation of energy balance. It contains two distinct subpopulations of neurons that express Ob-Rb as well as insulin receptors [62, 63]. One population expresses proopiomelanocortin (POMC), a precursor peptide that is processed in different tissues into a number of peptides, including alpha-melanocyte-stimulating hormone (α-MSH). α-MSH is an agonist for melanocortin-3 and -4 receptors (MC3R, MC4R), and inhibits food intake when injected into the hypothalamus [64]. Leptin increases expression of the POMC gene [63, 65], and also activates the POMC-containing neurons by direct depolarization [66], resulting in the synaptic release of α-MSH at other hypothalamic sites downstream of the ARC that contain MC3R and MC4R. The other population of ARC neurons with Ob-Rb produces the orexigenic peptides neuropeptide Y (NPY) and the endogenous MC3R/MC4R antagonist agouti-related protein (AgRP). Leptin reduces mRNA expression for NPY and AgRP [67], and hyperpolarizes these neurons [66], resulting in reduced synaptic release of these orexigenic/anabolic signals at other brain sites with MCR and a number of receptors for NPY. Thus, elevated leptin levels at times of energy surplus should directly activate pathways of arcuate origin that are anorexigenic/catabolic and reduce activity in orexigenic/anabolic pathways.

Important roles for melanocortin signaling in energy balance are demonstrated in mouse genetic knock-out models. Mice lacking the gene for POMC are hyperphagic, develop obesity when raised on a high-fat diet, and have altered pigmentation and defective adrenal development [68]. The heterozygotes have an intermediate phenotype between POMC (−/−) and wild-type controls, including leptin and corticosterone levels, suggesting a ‘gene dosage’ effect [68]. These phenotypes of obesity and other signs of POMC deficiency provide an animal model for similar syndromes caused by POMC mutations identified in humans [69]. Some genetic screens of obese humans suggest that the POMC gene is involved in some instances of common, non-POMC-syndromic obesity [70–72].

The roles of melanocortin receptor subtypes in energy balance are not yet completely clear. Mice lacking the MC3R are not hyperphagic, but are mildly obese due to effects on metabolism that result in increased fat mass and reduced lean body mass [73, 74]. The case is stronger for a particular relevance of the brain MC4R in energy balance. MC4R knock-out mice develop maturity-onset obesity with hyperphagia and increased linear growth. The heterozygotes have an intermediate phenotype between the homozygotes and wild-type controls so, as with POMC, there appears to be a ‘gene dosage’ effect [75]. In addition to hyperphagia, MC4R knock-out mice also have decreased oxygen consumption [74] suggesting that CNS melanocortin signaling affects metabolism in

peripheral tissues. Although some reports describe human MC4R mutations that seem to cause obesity in a dominant fashion [76], others report human MC4R mutations causing a loss-of-function suggesting haploinsufficiency rather than a dominant-negative mechanism [77]. In contrast to the rare mutations of genes for leptin, Ob-Rb, or POMC, MC4R gene mutations are more common, found in 3–5% of patients with a BMI of over 40 [78].

Obesity can also result from genetic inhibition of the activity at MCRs, in the presence of normal levels of POMC, α-MSH, and MCR. The agouti gene is normally expressed in the skin of mice, where the agouti protein product regulates pigmentation. Agouti causes obesity and diabetes when ectopically expressed as in the Ay mouse [79] and in transgenic models [80]. This is thought to occur through inhibition of brain MCRs. Indeed, transgenic overexpression of AgRP, the endogenous antagonist of MC4R in the brain, produces obese mice without altered pigmentation or adrenal insufficiency [81]. Central administration of the endogenous MC3R/MC4R agonist α-MSH or synthetic melanocortin agonists potently inhibit food intake in rodents [82, 83], whereas AgRP or synthetic melanocortin antagonists increase food intake when administered centrally [82]. Together, the data point to a number of levels at which the brain melanocortin system could be manipulated pharmaceuticals or with targeted gene therapy to treat human obesity, and this has been an area of intense industry effort.

Central administration of NPY potently stimulates feeding in a variety of paradigms [84–86], and repeated or chronic administration produces obesity [86, 87]. Brain administration of NPY decreases energy expenditure in rodents, primarily by decreasing thermogenesis in brown adipose tissue [88]. It also increases lipogenesis [87]. Hyperphagia and obesity in genetic and experimental models are associated with increased NPY-ergic signaling in the hypothalamus, via increased NPY gene expression and production [89–92] and secretion [93, 94], or increased NPY receptor abundance [92, 95]. Surprisingly, however, NPY and NPY receptor knock-out mice have normal levels of food intake and body weight, and have normal hyperphagic responses after fasting [96]. These results may simply reflect the fact that there are multiple, redundant systems that regulate energy balance, and that the absence of one of them is not always enough to lead to energy dysregulation. However, when NPY knock-out is carried out on an ob/ob background, the double-mutant mice are halfway between normal lean and regular ob/ob mice in body weight and fat mass [97].

Arcuate NPY/AgRP and POMC neurons project to the PVN [98, 99] and the lateral hypothalamic area (LH) [63], two nuclei involved in autonomic regulation. The PVN appears to play a major role in anorexigenic signaling, whereas the lateral hypothalamus seems to be more involved in stimulating or maintaining food intake. NPY receptor subtypes and MCRs are present on a number of

neuronal populations in the PVN [100, 101] and LH [101]. Changes in NPY and melanocortin signaling alter the expression of neuropeptides in the PVN [102–104] and changes in melanocortin signaling affect expression of neuropeptides in the LH [105] that affect energy homeostasis. The PVN contains multiple neuronal subtypes that make either oxytocin, corticotropin-releasing factor (CRF), thyrotropin-releasing hormone (TRH), or gastrin-releasing peptide (GRP), all of which lead to reductions in feeding [106–109] or increased energy expenditure [110, 111] when administered into the brain. The LH contains neurons that produce either orexins or melanin-concentrating hormone (MCH), both of which increase feeding when given centrally [112, 113]. As is the case with NPY and melanocortin signaling, targets at various levels of these neuropeptide systems are being intensively investigated for their potential for pharmaceutical or gene therapy for management of body weight.

Hypothalamic Neurons as Metabolic Integrators

As well as responding to circulating hormones such as leptin and insulin, and to the neuropeptide systems downstream of Ob-Rb and insulin receptor activation, hypothalamic neurons can respond to alterations in local nutrient concentrations. As the prime example, the brain depends upon on a constant supply of glucose to meet its metabolic demand [114], and integrated homeostatic systems have evolved to regulate glucose levels in peripheral tissues and in the brain. It has long been known that certain hypothalamic neurons alter their activity in response to changes in glucose concentration [115, 116]. Activity of glucose-excited (GE) neurons increases, whereas glucose-inhibited (GI) neurons decrease their activity, as ambient glucose levels rise. This is thought to occur in many GE neurons as the result of glucose uptake and its subsequent metabolism. Intracellular glucose is phosphorylated by the pancreatic form of glucokinase in many glucosensing neurons. Glucose metabolism leads ultimately to the generation of ATP, which binds to an ATP-sensitive K^+ channel (KATP). The channel closes, depolarizing the cell sufficiently to open voltage-gated Ca^{2+} channels, leading to action potentials and the release of neurotransmitters [reviewed in 117]. Less is known about GI neuronal glucosensing, although a Cl^- channel, the Na^+-K^+ ATP pump, and an ATP-responsive K^+ channel have all been proposed as possible final common pathways [117].

Glucosensing neurons may actually be ‘metabolic sensors’ in a broader sense. They can respond electrophysiologically to a variety of other metabolites such as lactate [118], ketone bodies [119], and free fatty acids [120]. Glucosensing neurons also express receptors for and respond to the adiposity signals leptin [121] and insulin [122]. Both leptin [121] and insulin [123] decrease action potential frequency in GE neurons, at least at high glucose concentrations, by activating KATP. Interestingly, long-chain fatty-acyl-CoA also

activates this channel [124], and inhibits glucokinase activity [125]. Thus, these neurons can integrate a variety of metabolic, hormonal, transmitter, and peptide signals related to metabolic status. Anabolic NPY neurons in the ARC are GI [126], and catabolic ARC POMC neurons are GE [127], and are prototypic examples of such metabolic integrators.

In regard to homeostatic responses to changes in physiological metabolic status, it has long been hypothesized that physiologic changes in glucose levels may regulate food intake [128]. Although evidence has been somewhat conflicting, it has indeed been shown that i.c.v. glucose administration decreases food intake and body weight [129, 130], and pharmacological glucoprivation in the brain [131] at glucose-sensing sites [132, 133] increases food intake. Consistent with the notion that the brain may also sense other nutrients to regulate energy balance, i.c.v. administration of oleic acid has been recently reported to inhibit food intake, as well as to reduce hepatic glucose output [134].

Role of Neuronal Energy State in Hypothalamic Metabolic Sensing: AMPK

It has been proposed that ultimately, these and other nutrients, metabolites, and adiposity and energy signals from the periphery affect whole-body energy homeostasis through their effects on brain intracellular levels of the high-energy molecule ATP [117, 135–137]. This may be via direct effects of the ATP molecule itself, including its interactions with KATP and other ATP-regulated ion channels, as well as its interactions with a number of metabolic enzymes. Recently, however, there has been great interest in how the ratio of ATP level to that of the lower-energy molecule, AMP, may serve as an important intracellular signal of metabolic status in the hypothalamus, via its interaction with the enzyme AMP-activated protein kinase (AMPK) [138, 139].

AMPK is a member of a family of metabolite-sensing protein kinases and is recognized as a key sensor of energy balance in peripheral tissues [140–142]. Increased cellular AMP/ATP ratio activates an AMPK-kinase, which then phosphorylates AMPK (pAMPK) [143]. In turn, the active pAMPK can alter cellular metabolism and gene expression via multiple mechanisms, resulting collectively in the inhibition of anabolic processes (including synthesis of fatty acids and triglycerides) and the stimulation of catabolic processes (such as fatty acid oxidation, glycolysis, and glucose uptake). These changes conserve and restore cellular levels of ATP [142, 144, 145]. Recent studies have focused on the role of AMPK in neuronal responses to alterations in energy status [138, 146–149].

Hypothalamic AMPK activity has recently been shown to have broad significance in the control of food intake [138, 139], and this has since been supported by other work [146, 148, 149]. Intracerebroventricular administrations

of the adiposity hormone insulin, the nutrient glucose, or the MC3R/MC4R agonist MT-II, all anorexigenic agents, decrease AMPK activity in the PVN, whereas the endogenous MC3R/MC4R antagonist AgRP, a potent orexigen, increases AMPK activity in the PVN [139]. Injection of the adiposity signal leptin directly into the medial hypothalamus inhibits AMPK activity in the ARC and PVN [139]. Expression of a constituitively active AMPK-α subunit in the hypothalamus is sufficient to increase food intake and body weight, and expression of a dominant-negative AMPK-α subunit is sufficient to decrease feeding and body weight [139]. Furthermore, inhibition of hypothalamic AMPK is required for the anorexigenic and weight-loss effects of leptin, because expression of constituitively-active AMPK prevents these outcomes [139]. Using a pharmacological approach, Kim et al. [138] demonstrated that i.c.v. administration of the AMP-mimetic AICAR (5-aminoimidazole-4-carboxamide-1-beta-*D*-ribofuranoside), that activates AMPK, increases food intake whereas compound C, an inhibitor of AMPK, decreases food intake. They also showed that manipulating fatty acid metabolism modulates neuronal energy status, and alters the activity of hypothalamic AMPK, to reduce food intake and body weight [discussed below].

Manipulating CNS Fatty Acid Metabolism Alters Hypothalamic Metabolic Sensing: C75 as an Example

Synthesis of fatty acids increases when energy is in surplus to produce triglycerides for storage. Conversely, during periods of energy deficit, fatty acid synthesis is reduced and triglycerides are catabolized to release the stored energy. C75 is a synthetic compound that inhibits fatty acid synthase (FAS), is a lipogenic enzyme that catalyzes the de novo synthesis of long-chain fatty acids in the cytosol [150]. C75 was designed to interfere with a site on FAS that covalently binds the substrates acetate and malonate, and thus C75 prevents elongation of the acyl chain [151]. C75 also interferes with malonyl-CoA binding to another enzyme, carnitine palmitoyltransferase-1 (CPT-1) [152]. This effectively disinhibits CPT-1, permitting the translocation of long-chain acyl-CoA into mitochondria where they undergo beta-oxidation, resulting in the generation of ATP [153]. C75 potently increases fatty acid oxidation and ATP levels in vitro [147, 152, 154] and increases whole-body energy production as indicated by an increase in VO_2 [155].

Effects of C75 on Hypothalamic Neuropeptides

C75 reduces food intake and causes significant weight-loss when given peripherally or i.c.v. at one-hundredth of the peripheral dose, suggesting that at least part of the effect of C75 is mediated centrally [154]. C75 alters gene expression for the transcription factor cFos selectively in hypothalamic nuclei

with known importance in the regulation of food intake and energy balance [156, 157], and alters gene expression of hypothalamic neuropeptides involved in energy balance. Even though C75 decreases food intake [154, 157, 158], it prevents the expected decreases in mRNA for POMC, precursor for the anorexigenic α-MSH [158, 159], and blocks the anticipated anorexia-associated increases in hypothalamic mRNAs for the orexigens NPY and AgRP [138, 152, 154–156, 158–161].

Molecular Mechanism of C75 Action: AMPK

The mRNAs for FAS enzyme and NPY are colocalized in neurons in the medial ARC, suggesting that C75 could act in a cell-autonomous manner to affect NPY expression [162]. C75 increases ATP levels in neurons in vitro [147], and in hypothalamus in vivo [138], with concomitant decrease in levels of AMP, reduced AMP/ATP ratio, and subsequent decrease in pAMPK [138]. The active, phosphorylated form of AMPK (pAMPK) phosphorylates and thereby activates cAMP response element binding protein (CREB, pCREB) [163]. C75, which reduces levels of pAMPK, reduces the level of pCREB in the ARC [162]. The cAMP-CREB pathway has been implicated in mediating the increase in NPY expression during fasting [164]. Consistent with C75's reductions of pAMPK and pCREB, C75 reduces NPY gene expression [138, 152, 154–156, 158–161]. Thus, C75's hypophagic action is proposed to work through this series of biochemical events to reduce orexigenic signaling.

Regulated Variable: Adipose Tissue, a Focus on Fat Metabolism

Manipulations of fat metabolism in the brain can alter energy intake. They might also affect energy expenditure by peripheral tissues. Researchers have recently reported that i.c.v. administration of the natural product FAS inhibitor cerulenin increases skeletal muscle CPT-1 activity [165]. They propose that part of the mechanism by which peripheral administration of cerulenin decreases body weight and adipose mass and increases heat production [166] involves cerulenin acting centrally, resulting in increased skeletal muscle CPT-1 activity and fatty acid oxidation. Notably, intrahypothalamic injection of leptin has been shown to increase fatty acid oxidation in skeletal muscle [167], and is one of a number of anorexigenic treatments recently shown to decrease hypothalamic AMPK activity [139], as the FAS inhibitor C75 does [138]. It is tempting to speculate that i.c.v cerulenin exerts its actions on peripheral tissue metabolism via a reduction in hypothalamic AMPK activity. Effects of central C75 administration on peripheral tissue metabolism have not yet been explored.

Acute systemic administration of C75 produces greater weight-loss than expected from the hypophagia alone [154], and chronic systemic C75 affects enzymes in white adipose tissue, liver, and skeletal muscle in ways that should increase fatty acid oxidation, and inhibit fatty acid synthesis and fat storage, resulting in weight-loss [152, 155, 168]. It is reasonable that compounds that decrease FAS activity will have direct actions in peripheral tissues to decrease fat accumulation [169]. However, C75 caused such a dramatic loss of hepatic fat in mice made obese with a high-fat diet, compared with the pair-fed control [154], that further studies were performed to investigate other potential mechanisms by which C75 could reduce fat depots. These studies demonstrated that C75, likely through its stimulation of CPT-1, increases fat oxidation, thus contributing to the profound weight loss seen with systemic administration of C75. This effect appears to be mediated by direct effects of C75 on adipose tissue and liver [152].

The pathways for fat synthesis and oxidation offer other potential enzyme targets for obesity treatments in addition to FAS and CPT-1. Acetyl-CoA carboxylase (ACC) is the ATP-requiring, rate-limiting step of long-chain fatty acid synthesis, just prior to FAS. ACC-1 and ACC-2 are encoded by different genes, and are differentially expressed. ACC-1 is present in cytosol in lipogenic tissues such as white adipose, ACC-2 is associated with the mitochondrial membrane in lipid oxidative tissues such as skeletal muscle, and both isoforms are expressed in liver [170, 171]. ACC activity is activated by citrate, and inhibited via phosphorylation by pAMPK [172]. ACC-2 knock-out mice show an elevated rate of fatty acid oxidation, and are resistant to diet-induced obesity. Their levels of uncoupling proteins are high in adipose, heart, and muscle, which together with the increased fatty acid oxidation may account for the upregulated energy expenditure [173, 174]. Inhibitors of mammalian ACC-1/ACC-2 have been shown to reduce triglyceride synthesis and increase fatty acid oxidation in rats [175]. Another candidate target for obesity treatment, the enzyme glycerol-3-phosphate acyltransferase (GPAT), catalyzes the initial step in the synthesis of triglyceride from glycerol-3-phosphate and fatty acids. Mice that are deficient in the gene for the mitochondrial form, GPAT-1, show decreased hepatic and plasma triglyceride levels as well as lower body weight than wild-type control [176]. GPAT-1 and CPT-1 are both located on the outer mitochondrial membrane. GPAT is thought to regulate the rate of fatty acid oxidation as a consequence of its own level of activity. In the absence of GPAT-1 in knock-out mice, fatty acids are thought to be shunted toward translocation by CPT-1 into mitochondria for beta-oxidation, rather than being used for triglyceride synthesis. The development of GPAT-1 inhibitors could help to test this hypothesis. Finally, in addition to the enzymes involved in the synthesis or oxidation of fats, there are a number of other enzymes involved in the digestion and absorption of

fat from the gastrointestinal tract (including Orlistat, one of only two drugs currently approved by the FDA for long-term treatment of obesity), as well as others that regulate fat storage in and mobilization from adipose tissue [reviewed in 177]. These may serve as additional pharmacological targets for obesity treatment.

Conclusion

The obesity epidemic poses a serious threat to public health. Effective therapies for obesity and long-term weight maintenance have been elusive. However, the recent advances in our understanding of the mechanisms that govern food intake and energy balance have revealed many potential points of intervention. This review has focused primarily on adiposity signaling and fat metabolism, and pointed to how these may impinge ultimately on the energy state of key metabolic sensors to regulate whole-body energy balance.

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Current Nutritional Treatments of Obesity

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Abstract

Obesity in our country is a growing concern. There are several different options for weight loss; however, individuals must be self-motivated and amendable to change in order to achieve success with their weight loss goals. Several strategies used by professionals in the US today to treat overweight and obesity, include diet therapy, exercise, behavior modification, pharmacotherapy, and surgery. The focus of the American Dietetic Association (ADA) Weight Management Position Statement is no longer just on weight loss but now on weight management. Reaching one's ideal body weight is recommended but not often realistic. Frequently, the goal of treatment shifts to maintenance of ones current weight or attempts at moderate weight loss. Lifestyle modification or behavioral modification interventions rely on analyzing behavior to identify events that are associated with appropriate vs. inappropriate eating, exercise, or thinking habits. Certain primary strategies that have been found to be useful for helping people change their behaviors so that they can lose weight and maintain their weight loss, include self-monitoring, stimulus control, cognitive restructuring, stress management, social support, physical activity, and relapse prevention. Weight loss programs should strive to combine a nutritionally balanced dietary regimen with exercise and lifestyle modifications at the lowest possible cost. There are several different methods used for dietary modifications; low calorie diets, very low calorie diets, fasting, formula diets and meal replacement programs, and popular diets. Bariatric surgery is gaining popularity as it has been an effective way to treat obesity. Following gastric bypass surgery, the patients must be prepared to modify their eating behaviors and dietary selections to assist with weight loss and prevent potential complications. Patients should be educated on the dietary guidelines extensively prior to surgery and again post-operatively.

Obesity is a disease that affects millions of people in the United States. Obesity is measured using body mass index (BMI). Body mass index can be calculated by obtaining a patient's height and weight and comparing it to the

BMI table. A person is considered overweight if he has a BMI of 25 or above; obese if he has a BMI of 30 or more, and clinically severely obese if he has a BMI of 40 or above [1]. About 97.1 million or 54.9% of adults in the United States are overweight. Additionally, about 39.8 million or 22.3% are defined as obese [2]. These numbers account only for adults; they do not include the dramatic rise in overweight and obese in children or adolescents.

Approximately 280,000 deaths annually in the US are estimated to be attributed to obesity [3]. Being overweight or obese increases a person's risk for developing several weight-related medical conditions. Some of the medical conditions include hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and endometrial, breast, prostate, and colon cancers [1]. Additionally, obese individuals may suffer from social stigmatism and discrimination. Even small decreases in weight could have positive health benefits in patients who have already developed co-morbid medical conditions [4]. Further, it has been shown that obese persons who lose even small amounts of weight (5–10% of initial body weight) are likely to improve their health by reducing the severity of the comorbidities associated with obesity. Even with a 10% or less weight reduction there was an improvement in glycemic control, blood pressure, and lowered cholesterol levels [1, 5].

This increase in the overweight and obese population has affected the US economy. In 1995, a total of USD 99.2 billion was spent on people that were overweight and obese, with USD 51.6 billion for direct costs and USD 47.6 billion for indirect costs [6]. Direct costs are defined as preventative, diagnostic, and treatment services and indirect costs as the value of wages lost by people unable to work because of illness or disability, as well as the amount of money lost by premature deaths. In the future, it is estimated that healthcare costs will be higher for persons who are obese [7].

The cause of the increase in persons overweight and obese is unclear, but likely multifactorial. Research has identified genetic, metabolic, biochemical, psychological, and physiological factors that may have contributed to obesity. Lifestyle patterns that play a role in obesity include the decline in smoking, a plethora of food choices, and decreased opportunities and motivation for physical activity [8]. The environment in which we live is one that promotes excessive food intake and discourages physical activity [9]. In this age of technological advancements, physical activity and the activities of daily living have been reduced.

The percentage of women and men trying to lose weight at any given time is 35–40 and 20–24%, respectively [10]. Americans spend more than USD 33 billion per year on weight control products and services, yet these efforts seem to have had little effect on slowing the increasing prevalence of obesity [11].

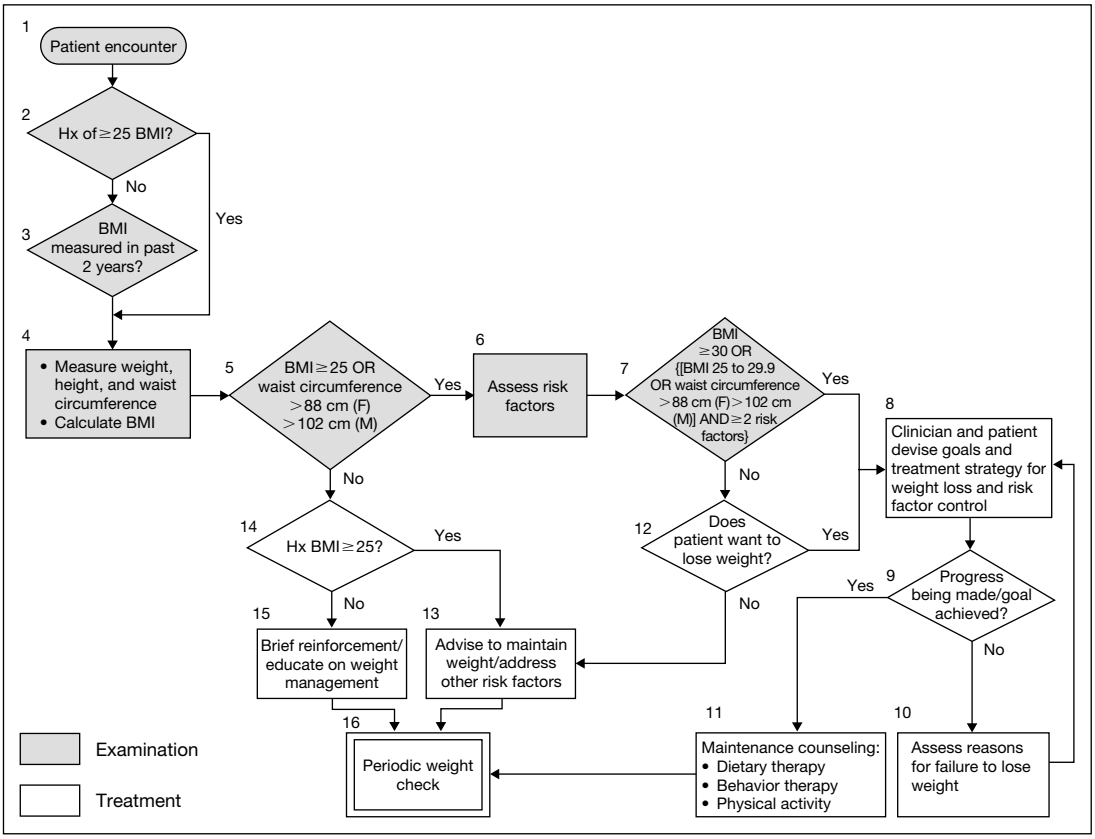

Fig. 1. Treatment algorithm. The algorithm applies only to the assessment for overweight and obesity and subsequent decisions based on that assessment. It does not include any initial overall assessment for cardiovascular risk factors or diseases that are indicated. From ref. [23].

There are several strategies used by professionals in the US today to treat overweight and obesity. Some of these include diet therapy, exercise, behavior modification, pharmacotherapy, and surgery. Figure 1 presents an algorithm for the management of obesity.

Despite these strategies, weight loss is hard to maintain over a long period of time (i.e. 3–5 years), with high rates of weight regain. This weight regain generally occurs unless a weight maintenance program consisting of dietary therapy, physical activity, and behavioral therapy is continued indefinitely [1].

Goals of Weight Loss Treatment

The focus of the American Dietetic Association (ADA) Weight Management Position Statement is no longer just on weight loss but now on weight management [12]. Reaching one's ideal body weight is recommended but not often realistic. Frequently, the goal of treatment shifts to maintenance of ones current weight or attempts at moderate weight loss.

Despite the well-documented benefits of moderate weight loss for obese individuals, the patients may have self-defined goal weights that differ considerably from the goals suggested by the health professionals [13]. Their weight loss goals and expectations are often unrealistic and not likely to be achieved. Health professionals must therefore work with the obese individuals and set more realistic goals with modest weight loss and explain the benefits associated with this loss. In addition to setting these realistic goals, a comprehensive approach involving dietary, behavioral, and biologic modifications should be included in the weight loss plan.

Behavioral Modifications

Lifestyle modification or behavioral modification interventions rely on analyzing behavior to identify events that are associated with appropriate vs. inappropriate eating, exercise, or thinking habits [14]. Behaviors and consequences should be evaluated to modify a situation. For example, if an individual finds that he or she overeats when stressed, then steps should be taken to help the individual alleviate stress in a more constructive way. Prior to initiating behavior modification therapy, the health professional must first establish a collaborative relationship with the individual that will facilitate adherence to treatment and elicit behavioral changes. There is evidence that this approach can improve the bond between patient and provider, thus reducing and improving overall outcome [15].

Certain primary strategies have been found to be useful for helping people change their behaviors so that they can lose weight and maintain their weight loss [16]. These strategies include self-monitoring, stimulus control, cognitive restructuring, stress management, social support, physical activity, and relapse prevention.

Self-monitoring activities include using food and activity diaries. These are useful in recording intake, frequency and duration of exercising, as well as situations where overeating might take place. Individuals are also encouraged to document their thoughts and feelings that accompany each entry. Self-monitoring helps illicit eating patterns, allowing the health professional and individual

to set up goals and help prevent relapses. Although individuals do not always report their dietary and exercise behaviors accurately, the primary purpose of self-monitoring is to make the individuals more aware of their obesity-related behaviors and the factors that influence this behavior [17]. Self-monitoring with food and activity diaries is one of the most helpful obesity management tools used today.

Stimulus control involves identifying the environmental cues associated with overeating and inactivity [16]. Learning how to control cues associated with overeating or inactivity can be very helpful for maintaining long-term weight loss because exposure to these cues may precipitate relapse [18]. For example, individuals are taught to decrease the rate at which one eats, thus becoming mindful of satiety cues and reducing food intake. Strategies such as putting down the utensils between bites, pausing during meals, and chewing for a minimum number of times are some ways to slow the eating process. Some lifestyle modifications are listed in table 1.

Cognitive restructuring teaches patients to identify, challenge, and correct the negative or unrealistic thoughts that frequently undermine their efforts. For example, many individuals criticize themselves after a dietary lapse which can in turn lead to total abandonment of their weight loss efforts. Teaching an individual to 'positive self-talk' can help him or her to deal more constructively with such scenarios [16]. For example, 'I had a candy bar after lunch. That one candy bar is not going to increase my weight. I will just try and eat healthy for the rest of the day and avoid the vending machine.' This is an example of positive self-talk.

Stress is a primary predictor of relapse and overeating [18]. Stress management includes teaching individuals other constructive methods for dealing with stress rather than eating. Some documented methods include diaphragmatic breathing, progressive muscle relaxation, and meditation.

Many studies have found that persons with higher levels of social support tend to do better in weight loss programs [18, 19]. This support can come from family members, support groups, religious groups, peers, or community-based programs. Peer support may be particularly useful because it helps individuals learn greater self-acceptance, helps develop interpersonal relationships, and helps manage stressful work or family situations [16].

Physical activity will be discussed in detail later in the chapter.

The last major strategy involves relapse prevention. This is one of the most important strategies in obesity management programs. Individuals should be taught that relapses are common and that recognizing and anticipating situations that might illicit these downturns are vital for prevention [20]. For example, many studies have found that negative emotions as well as certain social situations, such as travel or parties, promote anxiety and cause relapse [18]. Individuals must be taught how to manage these situations to prevent relapses.

Table 1. Lifestyle modification strategies

Elimination of eating cues
Eat only sitting down at one designated place
Sit in a different seat at the table
Leave the table as soon as eating is done
Do not combine eating with other activities, such as reading or watching television
Do not put bowls of food on the table
At a restaurant, limit intake from the bread basket to one roll with no or a small amount of butter
Stock home with healthier food choices
Keep all food in cupboards where it cannot be seen
Shop for groceries from a list after a full meal
Limit the amount of money taken when shopping
Plan meals and snacks
Plan for special events, parties, and dinners
Immediately place leftovers in storage containers and refrigerate or freeze them for another meal
Negotiate with the family to eat healthier foods
Ask others to monitor eating patterns and provide positive feedback
Substitute other activities for snacking
Snack on fresh vegetables and fruit
Behaviors to prolong eating and reduce the amount of food eaten
Eat slowly and savor each mouthful
Put down the fork between bites
Delay eating for 2–3 min and converse with others
Postpone a desired snack for 10 min
Serve food on a smaller plate
Leave 1 or 2 bites of food on the plate
Divide portions in half so that another portion can be permitted

Reprinted from J Am Diet Assoc 1988;88:1530.

Behavioral modification is an integral component to the success of obesity treatment. It is thought to be most effective when taught in group sessions (10–20 participants) over an extended period (20–26 weeks). The aforementioned strategies are reviewed during these sessions. Comprehensive lifestyle modification in weight control appears to be most effective for the mildly obese (20–40% overweight). It is noteworthy that despite behavior modification strategies, reviews have shown that individuals lose 9–10% of their starting weight but regain approximately one-third of the lost weight in the year following the treatment [21]. Weight regain is a problem regardless of the program or obesity management technique.

Dietary Modification

Weight loss programs should strive to combine a nutritionally balanced dietary regimen with exercise and lifestyle modifications at the lowest possible cost [1]. There are several different methods used for dietary modifications. Low calorie diets, very low calorie diets, fasting, formula diets and meal replacement programs, and popular diets. Regardless of the level of calorie restriction, healthful eating should be taught and emphasized, and recommendations for increasing physical activity should be included [22].

Low calorie diets (LCD) are designed to create an energy deficit of 500–1,000 calories a day and induce weight loss of 0.5–1 kg/week. The National Institutes of Health/National Heart Lung and Blood Institute, North American Association for the Study of Obesity (NHLBI/NAASO) guide recommends LCDs of 1,000–1,200 cal/day for most overweight women and 1,200–1,600 cal/day for most overweight men (and for women who exercise regularly or weight ≥75 kg) [23]. The LCD should be higher in carbohydrates (55% or more of total calories), with generous portions of protein (~15% of total calories). Fat content should not exceed 30% of total calories with no more than 8–10% of total calories coming from saturated fats. A Low-Calorie Step I Diet is shown in table 2.

Portion control is stressed and self-monitoring of calorie intake is necessary for the success of LCDs. Since underestimating and poor documentation is often a problem, individuals need to be instructed in reading food labels, measuring portion sizes, and recording their food intake as soon as possible after eating. The more self-monitoring records an individual completes each week, the more likely weight loss will be achieved [24].

Extreme energy restriction diets such as Very Low Calorie Diets (VLCD) and Fasting provide fewer than 800 cal/day or fewer than 200 calories/day respectively. Although VLCDs are typically recommended for individuals with a BMI ≥ 30 little evidence suggest that intakes fewer than 800 calories daily are of any advantage [25]. Most VLCDs have the following characteristics: they are hypocaloric but relatively high in protein (70–100 g/day); they are designed to include a full complement of vitamins, minerals, electrolytes, and essential fatty acids, but not calories; they are given in a form that completely replaces usual food intake; and they are given for a period of 12–16 weeks [25]. VLCDs first became popular in the early 1960s. The original VLCD resulted in several deaths but over time the formulation has been improved. These diets are also often called a protein-sparing modified fast (PSMF). The current PSMF formulas now contain complete proteins and some carbohydrates, are supplemented with vitamins, minerals and electrolytes, and are usually included as part of a complete multidisciplinary program [26]. Cardiac complications, including risk

Table 2. Low-calorie step I diet

Nutrient	Recommended intake
Calories	~500–1,000 kcal/day reduction from usual intake
Total fat	30% or less of total calories
Saturated fatty acid	8–10% of total calories
Monounsaturated fatty acid	up to 15% of total calories
Polyunsaturated fatty acid	up to 10% of total calories
Cholesterol	<300 mg/day
Protein	~15% of total calories
Carbohydrate	55% or more of total calories
Sodium chloride	no more than 100 mmol/day (~2.4 g of sodium or ~6 g of sodium chloride)
Calcium	1,000–5,000 mg/day
Fiber	20–30 g/day

Reprinted from [23].

of sudden death, are still a concern. Risks include potassium loss as well as loss of body protein, which is proportionately greater in the less obese than in the more obese [27]. The multidisciplinary team should monitor serum electrolytes and supplement when necessary.

VLCDs produce weight losses of 15–25% in 8–12 weeks [28]. However, due to the high cost of these programs (approximately USD 3,000) and findings of significant weight regain over the years, these diets are not as popular as they once were. Several randomized trials found VLCDs to be no more effective than LCDs 1 year after treatment [29]. Therefore, an expert panel convened by NHLBI recommended against using VLCDs for weight-loss therapy. Medifast (www.med.fast.net) and Optifast (www.optifast.com) are two examples of a VLCD program.

Fasting (<200 calories/day) for weight loss is very seldom recommended. It is typically initiated as a result of a religious belief or protestations, in addition to those attempting weight loss. It is rarely carried out for the time necessary to provide substantial weight loss. Initially 50% of the weight loss is water weight.

Popular Diets

There are a growing number of popular diets on the market that are used today. Diets are divided into categories based on their macronutrient content.

These categories include high-fat, low-carbohydrate diets, moderate-fat, balanced nutrient reduction diets, and low- and very-low fat diets.

High-fat, low-carbohydrate diets are probably the most popular diets used today. These diets consist of 55–65% fat, and <20% of calories from carbohydrates or <100 g of carbohydrates a day. Examples of these diets are *Dr. Atkins' New Diet Revolution, The Carbohydrate Addict's Diet, The Zone Diet, The South Beach Diet,* and *The New Glucose Revolution.* The rational behind these diets is that high carbohydrate intake causes a rise in blood sugar, which raises insulin levels in the blood. This leads to weight gain by increasing fat deposition and by increasing hunger. These diet books claim that most people that are overweight do not overeat. Instead, they feel that high-carbohydrate meals leave individuals less satisfied than meals that contain adequate fat, resulting in increased hunger, and increased food intake [30]. Advocates of these types of diets recommend stopping the 'vicious cycle' of carbohydrate addiction and restrict carbohydrates severely enough to produce ketosis [31]. Ketosis is a good indicator of fat mobilization. In this condition, blood glucose and blood insulin is reduced, and appetite is suppressed. The potential effects of low-carbohydrate diets on bone health, renal function, and cancer risk have not been well established. Further, these diets typically are not nutritionally adequate, are usually low in several vitamins and minerals, such as calcium and potassium, and very high in saturated fat, cholesterol, and animal protein. Overall, safety of low-carbohydrate diets has not been established and more long-term studies need to be conducted.

Moderate-fat, balanced nutrient reduction diets contain 20–30% fat, 15–20% protein, and 55–60% carbohydrates [31]. Examples of these diets include most of the commercial weight loss centers (*Weight Watchers, Jenny Craig, Nutri-Systems*) and *Volumetrics.* The rationale behind these diets is that weight loss occurs when the body is in a negative energy balance. The goal is to provide the greatest variety of food choices to allow for nutritional adequacy and compliance, while still resulting in a slow but steady rate of weight loss (ex. 1–2 lbs/week) [31]. Currently *Weight Watchers* uses two approaches: (1) Flex Plan: assigns points to each food. Each person has an individualized point budget to spend on any food they choose and the weight loss occurs if the person stays within the point budget. (2) Core Plan: control eating without counting points by focusing on wholesome foods such as vegetables, fruits, grains and starches, lean meat/poultry/fish, and low fat dairy [32]. With both approaches, dieters will find themselves choosing mainly high fiber, low-fat foods to stay within the guidelines. Several studies have shown that moderate-fat, balanced nutrient reduction diets reduce LDL-cholesterol, normalize plasma triglycerides, and normalize the ration of HDL/TC [33]. Further studies have shown that these diets reduce blood pressure [34].

Very-low-fat diets are those containing less than 10% of calories from fat and low-fat diets contain 10–19% of calories from fat [31]. Both are very high in carbohydrates and moderate in protein. Examples of these diets are *Dr. Dean Ornish's Program for Reversing Heart Disease* and *The Pritikin Program.* The original purpose of these diets was to help slow down and even reverse the effects of dietary fat and cholesterol on heart disease. However, as Americans became fatter, they changed their focus onto the program's effect on body weight [31]. These diets both promote lifelong changes in diet, exercise and lifestyle. Dr. Ornish also combines diet with other lifestyle changes including meditation, stress reduction, and smoking cessation [35]. The rationale behind these diets is looking at the calorie density of fat (9 cal/g) vs. carbohydrates and protein (4 cal/kg). Because fat provides so much more energy per gram, an effective diet can be one that controls the amount of this nutrient. Dr. Ornish's diet is vegetarian with primary focus on vegetables, fruits, whole grains, and beans. *The Pritikin Program* allows a limited amount of low-fat animal protein a day (no more than 3.5 oz of lean beef, fowl, or fish) [36]. There is a significant amount of data showing the correlation between high-fat diet and heart disease, and to a lesser extent increased risk of cancer. Studies have shown that low-fat and very-low-fat diets reduce LDL-cholesterol, and may also decrease triglyceride levels, depending on the diet composition [31]. Although these diets are very high in fruits and vegetables and whole grains, they are low in vitamins E, vitamin B_{12}, and zinc. Further, many people struggle with sustaining a very low fat vegetarian diet over an extended period of time.

One study compared Atkins, Ornish, Weight Watchers, and the Zone Diets and concluded that weight loss was the greatest when individuals adhere to the diet, regardless of what is tried [37].

Physical Activity

Physical activity is an extremely important component of weight management programs. Typically, a combination of aerobic and resistance training is recommended. Resistance training helps to increase lean body mass, thus increasing metabolic rate and the ability to utilize more energy intake. Aerobic exercise helps to utilize energy. Several studies have shown that exercise alone is not effective with weight loss without calorie restriction [38]. However, physical activity is one of the most important predictors of weight maintenance [39, 40]. It has been demonstrated that weight regain is significantly less likely to occur when physical activity is combined with any weight-reduction method [41]. Further, there are several psychological benefits (i.e. improved self-esteem and body image) with exercise that may be more beneficial in the

long run. Health care providers should emphasize the importance of physical activity regardless of weight loss. Regular physical activity can reduce the risk for many medical comorbidities associated with obesity [42]. Additionally even if an individual is obese, being physically active can reduce risk for mortality [43].

The key to the health and weight management benefits of exercise is consistency. Additionally more recent evidence shows that physical activity done at a moderate-intensity level can produce health benefits [44]. According to the CDC recommendations (www.cdc.gov/nccdphp/dnpa/physical/recommendations/), adults should strive to meet either of the following physical activity recommendations:

- Adults should engage in moderate intensity physical activities for at least 30 min on 5 or more days of the week.
  - Centers for Disease Control and Prevention/American College of Sports Medicine

  or
- Adults should engage in vigorous-intensity physical activity 3 or more days per week for 20 or more minutes per occasion.
  - Healthy People 2010

Whatever the selected exercise, it should be readily available, easy to perform, pleasant and affordable.

Bariatric Surgery

Bariatric surgery is another method of weight loss that is gaining popularity in our country today. This surgery is reserved for those with a BMI of 40 or greater or for those with a BMI of 35 or greater, who have comorbid conditions and acceptable operative risks [1, 22]. The types of surgery performed today are characterized into two major groups (1) restrictive surgeries, and (2) malabsorptive surgeries with or without restriction.

Restrictive procedures include the vertical banded gastroplasty (VBG) and the adjustable silicone-banded gastric banding (ASGB). These procedures achieve weight loss by restricting the total amount of food an individual is able to consume at one sitting. Those who undergo these procedures are required to eat very slowly and chew their food thoroughly. Failure to modify these eating behaviors may result in frequent vomiting and severe discomfort [45]. The restrictive surgeries are preferred for highly motivated individuals due to the amount of discipline required to succeed. Frequent snacking or poor food choices can sabotage the success of the surgery and result in weight regain. Close nutrition monitoring to assist with food choices and meal planning can

help a patient with successful weight loss. A typical meal pattern should consist of three high protein, well-balanced meals a day. Beverage consumption should occur at least one hour following the completion of the meal to keep the pouch full for a longer period of time. Alcohol and carbonation should be avoided and beverage choices should be calorie-free. Further, the patients are encouraged to take one multivitamin a day to help ensure adequate nutrition.

Malabsorptive procedures include the Roux-en-Y (RYGB), biliopancreatic diversion (BPD), and duodenal switch (DS). The RYGB which is both restrictive and malabsorptive, is considered the gold standard and the most common procedure done in the United States. Gastric bypass procedures vary by method of transaction (laparoscopic or open), length of Roux limb, size of stoma, and size of gastric pouch. There are three main mechanisms of weight loss with the RYGB. First there is a decreased stomach storage capacity, second, there is a reduced pouch emptying rate due to the creation of a 10-mm anastomotic gastrointestinal stoma, and third there is a bypassed duodenum and proximal jejunum. To prevent complications and deficiencies, patients must alter their dietary patterns and behaviors for life. With the restrictive component, the guidelines are similar to the VBG and ASBS dietary guidelines. Patients must eat slowly and chew their food well to prevent vomiting and severe pain in the pouch. Also, patients must consume beverages at least 30 minutes after meals to prevent vomiting or diarrhea, which in turn may make patients feel hungrier more quickly after a meal, thus leading to snacking between meals.

Due to the malabsorptive nature of this surgery, patients are at risk for developing deficiencies of iron, folate, vitamin B_{12}, and calcium [46, 47]. Iron deficiencies are common in women of child-bearing age, patients with a history of iron deficiency anemia, and in those noncompliant with their vitamin/mineral supplementation. Iron deficiency occurs in approximately 33–50% of cases [48]. This deficiency is usually a result of a decreased intake of dietary heme iron and a decreased acid level in the pouch. Lower acid levels inhibit the ferrous iron to be converted to the more absorbable form of ferric iron [49]. Further, the duodenum is bypassed which is the primary absorption site for iron. Patients at risk for iron deficiencies are recommended to take 40–60 mg of elemental iron per day postoperatively.

Folate deficiencies are much less common in RYGB patients occurring in only about 20% of the cases performed [50]. The majority of dietary folate is absorbed in the proximal small intestine which is bypassed. Further dietary consumption of folate-rich foods, such as fruits and vegetables, may decrease. Patients are recommended to take a daily multivitamin with 100% RDA to help prevent a deficiency.

Vitamin B_{12} deficiencies occur in about 26–70% of inadequately supplemented patients [51]. The consumption of vitamin B_{12} rich foods is often

decreased which can contribute to the deficiency. Furthermore, with a decreased acidic environment in the pouch, less free vitamin B_{12} is released to bind with intrinsic factor, resulting in overall less absorption in the ileum [49]. Patients are encouraged to take a sublingual form of vitamin B_{12} every day following RYGB surgery or obtain monthly injections to maintain adequate levels.

Calcium deficiencies and metabolic bone disease is another long term complication following gastric bypass surgery. Dietary consumption of calcium-rich foods is decreased and the absorption of calcium in the proximal intestine is altered which may contribute to this deficiency. Typically serum calcium levels are within normal limits when tested. This poses a concern because the bones release calcium into the blood to normalize serum calcium. Excessive release of calcium from the bones puts the patient at risk for osteoporosis. Literature recommends approximately 1,200–1,500 mg of calcium citrate a day to help prevent calcium deficiencies. Calcium citrate is the preferred form of calcium over carbonate because it does not require acid to break it down for absorption [52].

Postoperative Dietary Modifications

Following gastric bypass surgery, the patients must be prepared to modify their eating behaviors and dietary selections to assist with weight loss and prevent potential complications. Patients should be educated on the dietary guidelines extensively prior to surgery and again postoperatively. There are no standardized recommendations, and they vary amongst health care professionals. For the most part, patients are recommended to follow a modified consistency diet for several weeks postoperatively (table 3).

Patients are instructed to consume about 1/2 cup to 1 cup of food and eat six small meals a day for the first 6 months postoperatively. Following this, they are instructed to consume 1 cup of food per meal and aim for 3 meals a day. There are several foods that may cause discomfort following surgery and should be consumed with caution or avoided to prevent complications (table 4).

Protein requirements are high in order to assist with weight loss and prevent muscle breakdown. Patients are instructed to consume approximately 60–80 g of protein a day through food sources and liquid protein supplements. Dehydration is a concern; therefore patients are encouraged to sip on fluids all day in between meals, with a goal of 64 ounces of calorie-free, carbonation-free liquids a day. This may be challenging at the beginning, therefore patients are encouraged to monitor their urine to make sure that it remains pale yellow in color.

There are several lifestyle dietary and behavioral changes that a patient undergoing gastric bypass surgery must make in order to prevent complications and succeed post-operatively (table 5).

Table 3. Postoperative dietary progression following gastric bypass surgery

Stage 1: Clear liquids (sugar-free gelatin, low-sodium broth, Crystal Light®)
Stage 2: Full liquids (sugar-free yogurt, skim milk, sugar free pudding)
Liquid/pureed diet: (weeks 1–4)
Six small meals a day (2–4 oz) with fluids in between meals
High protein, low-fat, low sugar
Protein supplementation
Soft diet: (weeks 4–8)
Six small meals a day (4–6 oz)
Soft cooked vegetables, ground meats, soft fruits
Solids: (after week 8)
Reintroduce low-fat, sugar-free, high protein foods

Table 4. Common food intolerances postoperatively

Tough meats
Bread
Stringy vegetables
Membranes of oranges and grapefruit
Skins of fruits and vegetables
Dairy produces
Concentrated sugar and sweets
Fried foods and fatty foods

Table 5. Lifetime dietary and behavioral considerations

Eat slowly, take small bites, and chew thoroughly
Portion control (2–4 oz for 4 weeks; 4–6 oz for 4 weeks, never exceeds 8 oz)
Stop eating and drinking when full
48–64 oz fluid, 30 min after meals
High protein consumption (60–80 g/day)
Avoid high calorie and carbonated beverages
Vitamin/mineral supplementation for life (chewable form for the first month)
Choose low-fat foods only
Exercise as soon as medically appropriate

Special Concerns

There are other special concerns that patients must monitor postoperatively. These include nausea and vomiting, hair loss, and dumping syndrome. Due to the creation of the smaller pouch and the restrictive component of the surgery, nausea and vomiting can sometimes occur with rapid eating, overeating, or improper chewing. Many patients experience this discomfort at the beginning until they get used to eating with their new pouch. Hair loss is another concern postoperatively. Several patients experience hair loss around three to four months postoperatively continuing until about seven months postoperatively. The exact cause of this is unknown; however, it is thought to be caused by suboptimal protein intake.

Symptoms of dumping syndrome include shakiness, sweats, dizziness, rapid heart rate, and often severe diarrhea. Sugar and concentrated sweets are usually the main culprits for this syndrome, although drinking too soon after a meal can cause it as well. When a concentrated sweets or a sugar source is consumed, it is quickly 'dumped' into the intestines causing a high osmotic load. This causes a fluid shift from the blood into the small intestine producing diarrhea. This drop in blood volume may also cause the heart rate to increase. The patient may feel faint and need to lie down. The symptoms are often so severe that they can further motivate a patient to refrain from poor food choices and make the appropriate behavioral changes. Dumping syndrome varies from person to person and some individuals never experience it, even after eating highly concentrated sweets and sugar sources. All patients should be taught to read food labels and avoid sugars and hidden sugars that appear in the first three ingredients on a label. Natural sugars found in fruit, vegetables, and dairy are usually well tolerated; although, lactose intolerance is another common postoperative side effect. Lactose sensitive individuals are instructed to use Lactaid® products. Finally, weight regain is another special concern following gastric bypass surgery. It is imperative that each member of the bariatric surgery team educates the patients both preoperatively and postoperatively on the realistic weight loss expectations and together set weight loss goals. It should be stressed that this surgery is a tool to assist with weight loss and without lifestyle, dietary, and behavioral changes, they may not have the weight loss that they want and may possibly gain weight back.

Conclusion

Obesity in our country is a growing concern. There are several different options for weight loss; however, individuals must be self-motivated and

amendable to change in order to achieve success with their weight loss goals. The American Dietetic Association (ADA) Weight Management Position Statement (2002) states, 'Successful weight management for adults requires a life-long commitment to healthful lifestyle behaviors emphasizing eating practices and daily physical activity that are sustainable and enjoyable' [12]. By forming bonds with their patients, health professionals can help individuals achieve desired weight goals and maintenance.

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Pharmacologic Treatment of Obesity

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Abstract

Obesity is strongly associated with conditions such as hypertension, diabetes mellitus and osteoarthritis that have known adverse health outcomes. The rising prevalence of obesity threatens to overburden our health care system. As a result, the need for safe and effective treatment options is urgent. Unfortunately, pharmacologic treatment options have been disappointing either because of poor side effect profiles or limited long-term efficacy. Our goal is to review currently available pharmacologic treatments and the data supporting their use so that practicing physicians may better incorporate them into a comprehensive, long-term treatment strategy for their patients. We focus on orlistat and sibutramine as these are the two medicines approved by the FDA for long-term treatment of obesity. In addition, we review briefly agents approved for short-term use as well as agents such as zonisamide and topiramate which have shown some promise as weight loss agents in specific clinical circumstances. Finally, we highlight one medicine currently in phase III clinical trials, an endocannabinoid receptor antagonist. Given the overwhelming research focus on this disease, it is likely that the coming years will bring more treatment options, raising the chance that our patients will have meaningful and sustained weight loss.

The adverse health impact of obesity has long been recognized. As Flemyng [1] pointed out nearly 250 years ago, ‘Corpulency, when in extraordinary degree, may be reckoned a disease, as it in some measure obstructs the free exercise of the animal functions; and hath a tendency to shorten life, by paving the way to dangerous distempers’. The current epidemic of overweight and obesity has led to an unprecedented high prevalence in the US, with nearly two-thirds of the adult population at potential health risks from excess body weight.

The recognition of obesity as a disease has resulted in numerous attempts at controlling body weight through pharmacologic treatment. Perhaps the first drug treatment used was thyroid extract. Unfortunately, it was eventually clear

that doses required for weight loss produced hyperthyroidism and its associated undesirable catabolic consequences [2]. Since then several drugs have been employed that resulted in unacceptable side effects (e.g. dinitrophenol – cataracts and neuropathy; amphetamine – addiction potential; 'rainbow pills' containing digitalis and diuretics – several deaths; aminoxaphen – pulmonary hypertension; fenfluramine as part of the 'fen-phen combination – valvular heart disease) [3].

As of this writing, only two medications – orlistat and sibutramine – have been approved for long-term use (generally viewed to be 1–2 years) as a result of testing in randomized trials as required by the US FDA. The other medications we describe were approved before 1974 and did not undergo the type of rigorous evaluation in long-term studies required today. As a result, we will review data supporting the use of orlistat and sibutramine in some detail. In addition we will mention briefly medications approved only for short-term use, as well as medications that currently are being used for other indications but are also promising as weight loss drugs. The search for safe, effective pharmacologic treatment options for the obese patient is intense. We will close with some promising new therapies in advanced stages of clinical development.

Sibutramine

Sibutramine (Meridia) is an anorexiant, or appetite suppressant. It inhibits the reuptake of norepinephrine and serotonin, and more weakly, the reuptake of dopamine [4, 5]. Although classified as a schedule IV drug, it does not have significant abuse potential. Unlike fenfluramine, it does not induce the release of serotonin and has not been associated with pulmonary hypertension or valvular heart disease. Several short-term studies have established the efficacy of sibutramine in promoting weight loss in a dose-dependant fashion [6–8]. In addition, it may prevent the decline in energy expenditure that occurs during weight loss. It is given in doses of 5–15 mg/day and is FDA-approved for use in conjunction with a reduced calorie diet for both weight loss and weight maintenance. Common side effects include dry mouth, headache, constipation and insomnia. Increases in both blood pressure and pulse have been demonstrated and led to discontinuation of the drug in up to 5% of patients. Therefore, it is prudent to ensure that blood pressure is at least moderately controlled prior to initiating treatment. Because of the potential for adverse effects, sibutramine has come under increased scrutiny recently.

Longer-term weight control studies have been performed with sibutramine, and suggest its efficacy in helping attain weight loss [9–13]. In one randomized, controlled study assessing the efficacy of sibutramine in maintenance of weight

loss achieved after 4 weeks on a very-low-calorie diet, 86% of patients in the sibutramine group had lost at least 5% of pre-intervention weight, as compared to 55% in the placebo group. When considering how much of the weight loss achieved during the 4 week diet-only period was maintained at 12 months, 75% of subjects in the sibutramine group maintained 100% of the initial weight loss, as compared with 42% in the placebo group. Interestingly, after stopping treatment, the two groups were comparable for mean weight regain at one month, but at three months, the sibutramine group had regained significantly more weight (4.3 vs. 2.3 kg) [11]. Another study demonstrated at least 5% weight loss in 77% of patients taking sibutramine in conjunction with modest caloric reduction (~600 kcal). Subsequently, patients were randomized to receive either placebo or sibutramine. Over the succeeding 18 months, 43% of patients receiving sibutramine maintained their weight loss as compared to 16% receiving placebo [14]. As with most weight loss studies, attrition rates were high (50% in placebo group, 42% in treatment group) and about 50% of patients had the dose of sibutramine increased to 20 mg/day. In addition to weight loss, both of the above-mentioned trials showed significant improvements in triglyceride and HDL_c levels but not LDL_c. Also, other studies have demonstrated improvements in hyperuricemia, and, in patients with diabetes, glycemic control [13]. Another study, performed in adolescent obese subjects, found that the addition of sibutramine to a behavioral modification program resulted in significantly better outcomes [15]. Similarly, a 1-year study found that the addition of structured lifestyle modifications (caloric restriction with or without fixed portion meals) as a combined therapy with sibutramine resulted in more significant weight loss than sibutramine alone [16]. Studies such as these suggest that physicians who prescribe sibutramine (and likely any pharmacologic agent for weight control) will achieve better results in the setting of a comprehensive lifestyle modification program.

A recent meta-analysis of sibutramine trials included randomized clinical trials of patients with a BMI of 25 or greater undergoing treatment with a duration of at least 8 weeks [17]. For trials reporting data at 16–24 weeks, weight loss ranged from 3.4–6.0 kg and at 44–54 weeks, a mean difference in weight loss of 4.45 kg favoring sibutramine (over placebo) was found. The authors concluded that patients taking sibutramine had a 20–30% greater likelihood of losing at least 5% of their body weight than did patients receiving placebo. With respect to other outcomes, no evidence of significant improvements in mortality or morbidity from obesity-associated diseases was found. Blood pressure outcomes were variable. Heart rate was consistently increased by a mean of 4 beats/min. While fasting blood glucose and hemoglobin A1c decreased slightly, no consistent effect was detected on cholesterol or lipid measures. While no serious adverse events were noted, the rate of such events could be as high as 1.5 per 1,000.

Orlistat

Orlistat (Xenical) is an inhibitor of gastrointestinal lipases, preventing the hydrolysis of triglycerides into the absorbable free fatty acids and monoacylglycerols. Its systemic absorption is less than 1%, and therefore has no effect on systemic lipases [18]. It induces weight loss by reducing nutrient absorption, specifically, dietary fat, by up to 30% [19]. Several studies of 1–2 years' duration have established its efficacy in inducing moderate weight loss when compared to placebo (5.9–10 vs. 4.6–6.4%) [20–27]. Orlistat has also been shown to reduce the regain of weight [20, 28]. One such study enrolled 743 patients into a 4-week lead-in period on a slightly hypocaloric diet (caloric deficit ~600 kcal/day). Those completing the lead-in were randomized to receive orlistat 120 mg three times daily or placebo for 1 year in conjunction with a hypocaloric diet. During this period, the orlistat group lost 10.2% of their body weight as compared to 6.1% in the placebo group. After the first year, patients were reassigned to orlistat or placebo, but on a eucaloric (weight maintenance) diet. Those continuing on orlistat on average regained half as much weight as those who were switched to placebo. Those switched from placebo to orlistat lost an additional 0.9 kg compared with a mean regain of 2.5 kg in patients continuing on placebo [28].

Another study demonstrated the 'dose dependency' of this effect: subjects treated with the 120 mg dose of orlistat regained 35.2% of lost weight, those taking the 60 mg dose regained 51.3%, and those taking placebo regained 63.4%. The long-term studies have also demonstrated reductions in total and low-density lipoprotein cholesterol as well as systolic and diastolic blood pressure [24]. Fasting insulin levels have been shown to decrease and in diabetic subjects, a reduction in glycosylated hemoglobin [21, 22, 27]. Finally, it does not appear that orlistat is associated with adverse changes in resting energy expenditure [29].

Gastrointestinal side effects are common and in studies have led to discontinuation more often than placebo (9 vs. 5%). The symptoms include flatulence with discharge, fecal urgency, fecal incontinence, steatorrhea, oily spotting, and increased frequency of defecation [19]. Often the effects decrease with ongoing treatment. Concomitant use of natural fiber may reduce the incidence of these effects. Decreased absorption of fat-soluble vitamins has been shown, and the daily use of multivitamins (and in particular vitamin D) 2 h before or after an orlistat dose is suggested. Finally, orlistat may impair the absorption of lipophilic medications, and subtherapeutic plasma levels of cyclosporine have been reported [30–32]. As a result, in such patients dose changes and monitoring of drug levels may be needed.

A recently published meta-analysis identified 22 randomized controlled trials (RCT) reporting 12-month outcomes. It estimated the mean weight loss

for orlistat-treated patients compared with placebo treated patients to be 2.89 kg [33]. With respect to adverse events, gastrointestinal symptoms were common, as expected. No serious adverse events were reported in the RCTs, but the estimated rate of such events was as high as 3 per 10,000.

Combination Therapy

In a small study comparing sibutramine to orlistat it was found that sibutramine alone or in combination with orlistat was more effective in reducing weight than orlistat alone. In general, however, there are few studies comparing one weight loss drug to another [34].

Agents Approved for Short-Term Use

Benzphtemaine, phendimetrazine, phentermine and diethylpropion are all noradrenergic compounds approved for 'short-term' use, generally said to be less than 12 weeks. Benzphtemaine and phendimetrazine are listed under DEA schedule III, implying a higher risk of abuse than the others, which are schedule IV. Studies of these agents suggest a moderate decrease in weight when compared with placebo (2–10 kg). Few studies have evaluated longer term efficacy (that is, beyond 6 months). Of these agents, phentermine is probably the most widely used. While it was problematic when used along with fenfluramine, it has not independently been associated with valvular heart disease. Typical side effects include insomnia, dry mouth, constipation, palpitations, hypertension and euphoria.

Other Agents

Selective Serotonin Reuptake Inhibitors (SSRIs)

Although fenfluramine and dexfenfluramine have been withdrawn from the market, the positive effect on weight loss achieved with these agents suggests a potential role for selective serotonin reuptake inhibitors. While some studies suggest fluoxetine exerts beneficial effects on weight, resting energy expenditure and glucose intolerance, there appears to be minimal long-term efficacy [35, 36]. Importantly, in the case of fluoxetine, while patients lost more weight on a 60-mg daily dose in the first 6 months of treatment compared to placebo, in the subsequent 6 months, steady weight regain occurred while still on the drug [37]. Indiscriminate use of SSRI medications as adjuncts to weight loss regimens seems unwise.

Topiramate (Topamax)

Topiramate is a sulfamate-substituted monosaccharide currently approved for adjunctive treatment of partial onset seizures or generalized tonic-conic seizures, and for seizures associated with Lennox-Gastaut syndrome [38]. The mechanism of action as an anti-convulsant involves blockade of voltage-activated Na^+ channels, enhancement of GABA-evoked currents, inhibition of kainite-evoked currents, inhibition of high-voltage activated Ca^{2+} channels, and inhibition of carbonic anhydrase [39]. Studies in rodents suggested an effect in inducing weight loss [40]. It was also observed that topiramate may mitigate weight gain observed with anti-depressant use [41]. Based on these observations, three-randomized controlled studies of weight loss have been published [42–44]. Bray et al. [43] conducted a dose-ranging study that found 6.3% weight loss in the two higher dose groups (192 and 384 mg/day), which was significantly greater than placebo (2.6%); also, at 24 weeks a plateau had not yet been reached. Wilding et al. conducted a longer-term study in which patients losing 6% or more of body weight during an initial run-in phase were excluded. Subsequently, a modified-intention-to-treat analysis showed weight loss of 9.1% in the group treated with 192 mg/day compared to 1.7% weight loss in the placebo group at 60 weeks. Finally, Astrup and colleagues analyzed the efficacy of topiramate in maintenance of weight loss [42]. In this study, during an 8-week dietary run-in period, subjects lost 10–11% of initial body weight. Subsequent to that, patients treated with placebo regained 1.8% of initial weight and those treated with topiramate lost an additional 5.2–6.4%. These latter two studies were terminated early because of discontinuation of immediate-release formulations in an effort to develop a new controlled-release formulation. A recent meta-analysis reviewed these and other studies [33] and concluded that the total percentage weight lost in topiramate-treated patients was 8% with significant heterogeneity among studies. It appears that paresthesias and changes in taste are much more common in topiramate treated patients (odds ratio of 20.18 and 11.14, respectively) [33]. In addition, other GI and CNS side effects appeared more commonly. No serious adverse events were reported in the studies to date.

We are wary of the above-noted side effects, but, in the appropriate clinical setting, topiramate may play a significant role in helping reduce weight (for example, in obese patients undergoing treatment for depression).

Zonisamide

Zonisamide is a sulfonamide currently approved as an antiepileptic, an effect believed to be mediated by blockade of sodium and calcium channels.

However, zonisamide also has dopaminergic and serotonergic effects and produces mild inhibition of carbonic anhydrase. It is possible that these latter mechanisms enhance its function as an appetite suppressant. One 16-week randomized, controlled trial involving 60 patients (mostly women) showed a 6% weight loss compared to 1% weight loss in placebo treated patients [45]. 36 patients completed an additional 16-week extension phase of the study with mean total weight loss of 8 kg. In terms of adverse outcomes, only fatigue was significantly increased when compared to placebo. However, in epilepsy studies, dizziness, somnolence and cognitive impairment have been reported frequently. Though rare, kidney stones and hematologic events have also been noted. Increased serum creatinine can also occur [45].

Longer-term studies are needed to confirm these findings. Similar to topiramate, zonisamide may have a role in selected patients based on their other co-morbid conditions.

On the Horizon: Rimonabant

The term endocannabinoids was coined after the discovery of membrane receptors for delta-9-tetrahydrocannabinol and endogenous ligands [46]. The elucidation of this system with endogenous ligands and two G-protein coupled receptors (CB1 and CB2) has led to the development of a novel class of drugs aimed at treating obesity and related metabolic disorders. The endocannabinoid system has been implicated in the physiologic control of energy balance and in glucose and lipid metabolism through both central orexigenic drive and peripheral lipogensis [47]. In addition, the endocannabinoid system has been suggested to form part of the neural circuitry regulated by leptin [48]. Rimonabant is the first of this new class of drug to have been studied in a clinical trial [recently published]. The rationale for drug development lay in the demonstration of overactivation of the endocannabinoid system in genetic models of obesity and in response to excessive food consumption [48]. Furthermore, the CB1 knock-out mouse is lean and resistant to obesity induced by high-fat feeding [49]. Finally, pharmacologic blockade of CB1 with rimonabant in obese animals produces weight loss and improves metabolic abnormalities [50]. Conversely, activation of the CB1 receptor stimulates hepatic fatty acid synthesis and promotes diet induced obesity [51].

Recently, Van Gaal et al. [52] have reported 1-year data from the 1,507-patient Rimonabant in Obesity-Europe trial. Rimonabant 5 and 20 mg/day produced a weight loss of 4.8 and 8.6 kg, respectively, compared to 3.6 kg weight loss in placebo-treated patients. In addition, the 20 mg/day group had a statistically significant reduction in waist circumference (8.5 cm). The proportion of

patients achieving greater than 10% weight loss was 27.4% in the 20 mg/day group compared to 7.3% with placebo. This 20 mg/day treatment group also had small but significant reductions in LDLc, triglycerides, HOMA-IR values, and increases in HDLc. The incidence of adverse events was slightly higher in the 20 mg/day group compared to the 5 mg/day or placebo groups, with the most common being nausea, dizziness, diarrhea and arthralgias. It was felt that these were mild and mostly transient side effects. Rimonabant represents a promising new treatment and (at this writing) is undergoing evaluation for FDA approval. Other CB1 antagonists are also under development. Readers are advised to watch for more data about this novel class of medication for weight control.

Overall, pharmacologic treatments have come a long way since the days of the amphetamines, but are still prone to unexpected side effects and poor long-term efficacy. While combinations of medications will undoubtedly be more effective than individual agents, as was seen in the development of drugs to control hypertension, trials of drug combinations for weight loss are rare, and have the potential to cause worse side effects than the individual agents alone. Further, pharmacologic alteration of eating behaviors is more complicated than alteration of physiologic parameters such as blood pressure, because many patients do not eat excessively because of excessive hunger, but rather because of habits and desire to eat.

Despite troublesome side effects and modest treatment effect, the currently available pharmacologic treatments offer hope that not only can weight loss be achieved, but that such weight loss may lead to amelioration of obesity-related comorbidities. Research on pathways that control energy balance is very active and drug development similarly so. This combination promises to offer more options to practioners interested in helping their obese patients lose weight. Similar to the situation with diabetes treatment, when several useful new treatment options became available in the 1990s, we have every hope that the coming decade will offer more treatment options for obesity and its comorbidities. Such progress will be accompanied by the need to individualize the medication to the patient as part of a comprehensive program. Perhaps most important is the need to treat obesity similarly to the way in which we treat hypertension and diabetes – as a life-long problem requiring long-term, regular follow-up.

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Bariatric Surgery

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Abstract

Bariatric surgery is currently the only effective long-term treatment of morbid obesity and its related co-morbidities. Gastric bypass, adjustable gastric banding, and duodenal switch with biliopancreatic diversion are the three most common operations performed in the United States to induce sustained weight loss. Patient selection is important since compliance postoperatively leads to a successful outcome in over 80% of patients. Preoperative psychological and behavioral problems may lead to maladaptive eating habits postoperatively that defeat the purpose of the surgery. To date, we do not have a 100% reliable method of profiling patients who will fail to keep weight off for the long term. It is therefore important that patients who have preoperative psychological problems that may lead to failure to lose or keep weight off after surgery are offered postoperative counseling along with group support.

Obesity is now the number one health crisis in the United States. In 2001, the prevalence of obesity among US adults was 21%, which reflects a 61% increase since 1991. Over 44 million Americans have a body mass index over 30 and these statistics are continually being revised with an upward trend. To date, there is no adequate medical therapy for the morbidly obese. Over 50 billion dollars are spent each year treating medical diseases directly related to obesity and an additional 30 billion dollars are spent per year on dietary programs and products. Severe obesity is associated with a variety of health problems including non-insulin-dependent diabetes, hypertension, cardiovascular disease, pulmonary dysfunction, osteoarthritis, gallbladder disease and specific malignancies such as breast and colon cancer. Psychological disorders including depression, eating disorders, distorted body image and low self-esteem are

common in those afflicted by morbid obesity. In the United States, the Center for Disease Control estimates the yearly death rate from obesity at 300,000 which currently trails behind smoking-related death rates of over 400,000. This is put into stark comparison when one considers the combined death rates from lung, colorectal, prostate, breast cancers plus AIDS is estimated at 295,000 a year by the CDC [1].

The majority of obesity-related co-morbidities could be reversed or prevented with significant and sustained weight loss. Unfortunately, traditional medical management including specialized diets, behavioral modification and anorectic (appetite suppressant) drugs have had little success in the severely obese population with only 5–10% of patients able to achieve long-lasting significant weight reduction. The current surgical procedures for obesity, however, have been found to be effective long-term and result in weight loss of at least 50% of excess body weight in 80–90% of patients. For this reason, surgery has become an increasingly important option in the management of severe obesity.

Patient Selection

In 1991, the NIH developed a consensus statement endorsing obesity surgery as an effective means of long-term weight control and specified criteria to be used in patient selection. To be considered a candidate for obesity surgery patients must be severely obese with a body mass index of greater than 40 (BMI = wt. (kg)/ht. (m^2)). This is equivalent to about 100 lbs or more over ideal body weight. Less obese patients with a BMI between 35 and 40 may also be candidates if they have an obesity-associated co-morbidity such as sleep apnea, diabetes, or coronary artery disease to name a few [2]. In general, patients should have failed previous attempts at supervised weight reduction programs and have realistic expectations about the long-term outcomes achieved with surgery. Chronological age, previous abdominal procedures, or previous failed obesity surgeries are not necessarily contraindications. Adolescents and those over 65 years old represented two groups that may benefit from morbid obesity surgery but not enough long-term outcome data has been accumulated to date. Adolescents should have attained a majority of their skeletal maturity (generally over 13 years of age for girls and over 15 years of age for boys) and should be involved with a multidisciplinary weight management center [3].

Most centers involved in obesity surgery emphasize the importance of a multi-disciplinary approach to patient screening and education. At Johns Hopkins, patients are initially evaluated by the operating surgeon, a dietitian, and a psychiatrist. Also, a monthly support group is offered for patients to attend.

Psychological Factors

Currently, there are not enough empirical data to standardize the preoperative evaluation of a morbid obese patient considering surgery. It is important that the patients have realistic expectations regarding surgery and understand that the decision to undergo surgery will be accompanied by life-long dietary changes. In addition, patients and their families need to be counseled on the potential psychosocial impact of rapid sustained weight loss as well as the possible long-term medical complications of obesity surgery.

Maladaptive eating behaviors preoperatively may lead to poor compliance with postoperative diets required after obesity surgery. There are currently no long-term studies to conclusively say how patients who have binge-eating behavior preoperatively will do after obesity surgery. A few studies have shown a worse outcome as far as excess weight loss, where other studies have shown the majority lose their binge behavior [4–6]. 'Grazing,' an eating behavior seen preoperatively in morbidly obese patients, may be seen in postoperative patients who develop a maladaptive eating behavior that defeats having a small gastric pouch where early satiety is the number one goal. Patients may consume a large amount of calories by grazing on carbohydrates, such as potato chips, that leaves the patient hungry and wanting more, which is followed by weight regain [7].

A patient with a current substance addiction is a contraindication to surgery. Alcohol may be more rapidly absorbed after surgery and could lead to a dangerous intoxication in the addicted patient. The extent that food and eating help addiction-prone patients soothe and comfort themselves may need to be addressed postoperatively.

Operative Procedures

A variety of surgical procedures have been developed to achieve weight loss. The initial procedures involved bypassing large amounts of small bowel that led to weight loss by severe malabsorption. The flaws in these small intestinal bypass operations were they had large segments of bowel that had neither food nor bilio-pancreatic fluid flowing through it. They, therefore, were stagnant which led to severe complications in many patients. These operations are therefore no longer done. A purely restrictive operation, which involves partitioning the stomach into a small upper reservoir so that the patient feels full with a small amount of food, has undergone several types of revisions since the 1980s. A high failure rate was seen due to staple line breakdown in a partitioned only stomach that left a small channel connecting the upper and lower stomach. A combination of restrictive with malabsorption is the most common type of

procedure done in the United States in the form of a Roux-en-Y gastric bypass. It is estimated that over 100,000 gastric bypass operations were performed in 2004 in the US, which is a major shift upward in these operations from 1998 when only approximately 25,000 cases were performed. All of the operations can be performed laparoscopically through smaller incisions and, therefore, decrease the chance of an incisional hernia and wound-related problems seen when using the open technique.

Vertical-Banded Gastroplasty

Vertical-banded gastroplasty (VBG) is a restrictive only operation that involves creating a small gastric reservoir or pouch measuring 15–20 ml in volume which then empties into the residual stomach via a calibrated and banded outlet. The primary advantages of VBG are the avoidance of malabsorption and the preservation of normal gastroduodenal continuity. On average, patients lose 40–50% of their excess body weight over the first 1–2 years. The main drawbacks of VBG, however, are that over time the pouch can expand, the marlex band can migrate or cause outlet obstruction, and the stomach staple line partitioning tends to breakdown. The re-operation rate for these complications is almost 30%. Although VBG is now only performed by a few centers in the country (most centers see it as an inferior operation with too many complications). Patients are now presenting with complications of VBG operations performed 5–10 years ago. Weight regain several years after surgery is typically due to a breakdown of the vertical staple line and patients report new dietary freedom. Revisional surgery and conversion to a gastric bypass usually results in durable weight loss but can be associated with a higher rate of perioperative complications.

Gastric Bypass

Since the early 1990s the gastric bypass procedure (GBP) (fig. 1) has largely replaced VBG as the operation of choice at most centers for obesity surgery. This procedure involves creating a small gastric pouch 20–30 ml in volume along the lesser curvature and then performing a gastrojejunostomy utilizing a Roux-en-Y limb of jejunum to allow the pouch to empty. Currently, it is performed both by open abdominal surgery or laparoscopic surgery [8]. The operation works by creating a small gastric reservoir, which limits intake, and also by inducing a moderate degree of malabsorption since the duodenum and proximal jejunum are bypassed. The gastrojejunostomy can also create a dumping-type syndrome and this helps patients to avoid sugary liquids postoperatively. The expected weight loss with the gastric bypass operation averages 70% of excess body weight with maximal weight loss occurring by 2 years

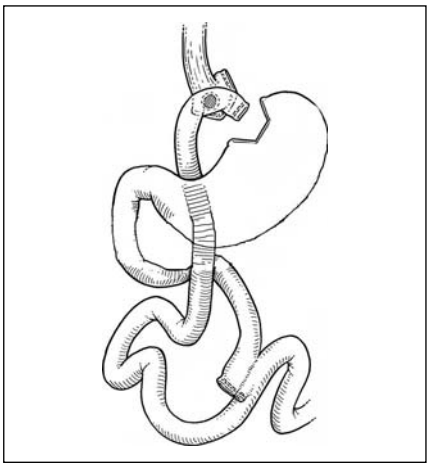

Fig. 1. Roux-en-Y gastric bypass.

postoperatively. Several randomized prospective studies have demonstrated superior weight loss with gastric bypass compared to VBG and that weight loss is sustained with long-term follow-up of over 15 years [9]. Most importantly, numerous studies have demonstrated that obesity-related diseases such as diabetes, hypertension, and sleep apnea are dramatically reversed within the first year of surgery. Multiple studies have shown that 70–80% of patients resolve their type II diabetes [9].

Laparoscopic Adjustable Gastric Banding

Laparoscopic adjustable gastric band received FDA approval in 2002, and has been in clinical use in the US since that time (fig. 2). The procedure involves placing a silastic band around the proximal stomach creating a 5- to 15-ml pouch and a narrow adjustable outlet. Similar to the VBG, the operation is purely restrictive. It is adjustable by injecting saline into a subcutaneous reservoir, which changes the volume of fluid in the band, thereby tightening its constriction around the upper stomach. This will create a small stomach reservoir above the band and decrease the flow of food through it, which should lead to early satiety. The VBG and GBP operations are essentially a 'one size fits all approach' with no adjustment potential.

Theoretic advantages of the gastric band are relative ease of placement, the absence of staple lines, and adjustability. Patients also seem to take comfort that the adjustable gastric band can be removed with relative return to a normal functioning stomach. Since they suffer from a chronic disease (morbid obesity) the vast majority will regain their weight if the band is removed. In general,

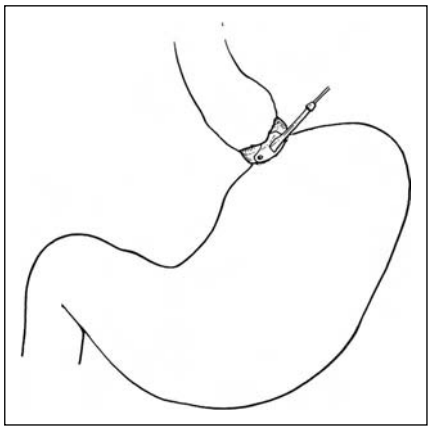

Fig. 2. Adjustable gastric band.

weight loss approaches 37–50% of excess body weight, similar to the VBG but less than gastric bypass. It has virtually replaced the VBG operation for patients who want a restrictive-only operation. Complications primarily involve band migration, erosion, malfunction, and slippage (stomach herniating through the band). The need for re-operation may be as high as 30%, as reported in an initial US trial but improvements in the design of the band and newer placement techniques appear to be reducing complications. Although the gastric band has enjoyed widespread acceptance and implementation in Europe, its role in North America remains to be determined. Sweet eaters who derive greater than 25% of their daily calories have been shown to do worse in a prospective randomized trial with a pure restrictive operation (VBG) vs. a restrictive and malabsorption combination operation (GBP) [10]. This may in part be due to dumping syndrome, which can cause abdominal pain if the patient eats sweets after gastric bypass. It may also be in part due to gut hormones, such as ghrelin, an appetite stimulant. Gastric bypass allows food to bypass the fundus of the stomach, where a significant amount of ghrelin is secreted when a patient diets. Ghrelin levels increase with dieting in the morbidly obese but stay the same when losing weight after gastric bypass [11].

Duodenal Switch with Biliopancreatic Diversion

The duodenal switch biliopancreatic diversion procedure (DS/BPD) achieves weight loss primarily through malabsorption. A distal (80%) gastrectomy is performed providing a small amount of restriction to oral intake. The distal small bowel is divided 250 cm proximal to the ileocecal valve, and the proximal bypassed bowel is anastomosed end-to-side to the ileum 100 cm from

the ileocecal valve. The resultant malabsorption of nutrients usually leads to weight loss of up to 80% excess body weight. Severe protein-calorie malnutrition, fat-soluble vitamin deficiencies, diarrhea, and osteoporosis are potential complications of the procedure. For this reason, close long-term follow-up and patient education regarding possible nutrient and vitamin deficiencies are essential.

Outcomes and Complications

After gastric bypass surgery, patients are usually seen in the clinic at least 4 times in the first year and then every 6–12 months thereafter. The preoperative weight of patients operated on at the Johns Hopkins Obesity Surgery Center averages 348 lbs with an average BMI of 56. Excess weight loss by 2 years postoperation averages 64–70%. This weight loss is accompanied by significant improvement in most obesity-related medical diseases including complete resolution of diabetes (75%), hypertension (73%), sleep apnea (90%), and gastroesophageal reflux (90%). Hepatic abnormalities such as nonalcoholic steatohepatitis are also improved with weight loss.

The main complications of gastric bypass surgery are primarily seen in the perioperative period. Mortality is usually less than 0.5% and primarily attributable to pulmonary emboli or sepsis secondary to anastomotic leakage. Vitamin B_{12} and iron deficiency can present as late complications and may require oral supplementation. All patients need to take multivitamins postoperatively and need to be followed at regular intervals for nutritional assessment. About 10–15% of the patients will either fail to achieve significant weight loss ($>$50% excess weight loss) or regain a significant amount of their lost weight after 2–3 years. These patients may respond to revisional surgery by increasing the amount of bypassed bowel to augment malabsorption. However, the root cause is usually due to grazing on carbohydrates, such as potato chips or other snack foods that does not cause a full sensation and has high caloric content.

In general, the results of gastric bypass surgery are excellent with the majority of patients losing greater than 50% of their excess body weight for the long-term. Obesity-related morbidities such as diabetes and hypertension are either reversed in the first year after surgery or prevented from developing. In experienced hands, the complications of surgery are acceptable with a mortality of less than 1% and a perioperative morbidity of less than 15%. A multidisciplinary approach to preoperative evaluation and postoperative follow-up is important to achieve long-term success. It is important for insurance companies and health care providers to understand that obesity surgery is not designed to

achieve a cosmetic result, but rather to improve the patient's overall medical health and prolong life. Patients need to be aware that although most operations are reversible, obesity surgery should be viewed as a life-long commitment with the need for long-term dietary changes, behavioral modification, and medical supervision [12].

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Body Contouring following Massive Weight Loss Resulting from Bariatric Surgery

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Abstract

A sharp increase in bariatric surgery has resulted in spike in the population of patients seeking body-contouring procedures. Skin and soft tissue redundancy of the trunk, buttocks, breasts, upper arms, and thighs following massive weight loss is unsightly and results in medical problems such as musculoskeletal strain from increased tissue weight, intertrigo or functional limitation with walking, maintaining adequate hygiene, bowel and bladder habits and sexual activity. These elements compound the inherent psychosocial issues related to massive weight loss. Using time-tested plastic surgical techniques, several operations have been designed and perfected to address the needs of these patients. These include breast, thigh and lower body lift, abdominoplasty, face and neck lifts as well as brachioplasty or arm lift. Recognizing that there is a qualitative as well as a quantitative difference in the type and amount of tissues in postbariatric patients these techniques have been suitably refined to optimize outcomes and provide safe and durable re-contouring. Consequently, bariatric surgery and the subsequent weight loss require an additional 2–3 years commitment towards body contouring procedures. Restoring their body image through reshaping procedures is an integral part of completing the treatment of post-weight-loss patients. Strategic skills in terms of assessment of each patient, careful planning, timing, especially for patient safety and technique are fundamental for the success of these often complex and extensive procedures.

Severe obesity is a chronic condition that is resistant to diet and exercise modulation alone [1–6] (table 1). Gastrointestinal surgery, which promotes weight loss by restricting food intake and, in some operations, interrupting the digestive process, is the best option for these patients thereby preventing serious obesity-related health problems.

Table 1. Obesity – definitions

Body Mass Index (BMI)
BMI = weight (kg)/height $(m)^2$
Definition of obesity
BMI >25 = overweight
BMI >30 = obese
BMI >40 = morbidly obese or 100 lbs in excess of ideal body weight (IBW)

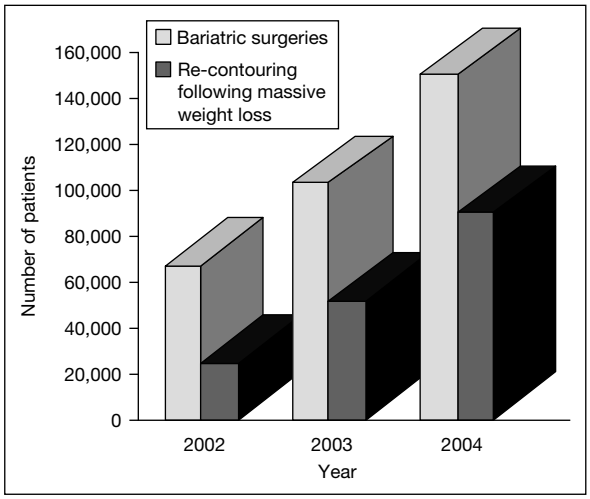

Fig. 1. Increasing trend towards bariatric operations as well as those undergoing recontouring surgery thereafter.

An effective long-term treatment for morbid obesity, bariatric surgery has revolutionized the treatment of morbid obesity. After bariatric surgery, new problems such as hanging redundant skin and soft tissue create a poor body image affecting the patient's quality of life and social acceptance to virtually the same degree as prior to the bariatric operation.

The increasing use of gastric bypass surgery to treat morbid obesity has resulted in a corresponding influx of patients requiring plastic surgery procedures to contour their body after massive weight loss (MWL) [7–13].

As seen in figure 1, more than 103,000 people underwent gastric bypass surgery in 2003, compared with 67,000 patients who had the surgery in 2002, according to the American Society for Bariatric Surgery. Similarly, over 52,000 body contouring procedures following MWL were performed in 2003, with a

40% increase in 2004. Responding to a survey by the American Society of Plastic Surgeons (ASPS), 94% of plastic surgeons reported that in the past 5 years the number of people seeking body contouring plastic surgery procedures following MWL had dramatically increased in their practices.

The three most common surgical procedures performed are abdominoplasty, breast surgery and brachioplasty (upper arms) [7, 14–17]. These are followed closely by middle thigh lift and, to a lesser degree, facial rejuvenation. As the demand for plastic surgery following MWL continues to grow, refined techniques and new technologies will continue to be developed. The number of patients undergoing buttock lifts increased by 74%; upper arm lifts, 66%; thigh lifts, 33% and lower body lifts, 14%. The most dramatic changes over the past 3 years include a 19-fold increase the incidence of brachioplasty and a 24-fold increase in lower body lifts performed.

Surgical Management

Reconstructive Surgical Principles

The objective of body contouring procedures is to redistribute and recontour areas of the body where excess skin (and some soft tissue) becomes redundant following MWL after bariatric surgery (gastric bypass surgery and other procedures). Patients present with either a generalized or local area of excess tissue in certain well-characterized areas such as the abdomen, breasts, arms, thighs and buttocks. Many postbariatric surgery patients also experience an extreme loss in skin elasticity that leads them to have body recontouring procedures, which greatly differ from contouring procedures performed on normal-weight patients. After recontouring, these patients' skin will still loosen and sag much faster with age. Patients undergoing bariatric surgery lose massive weight in a short period of time. Due to the rapidity of weight loss, as well as other factors, the quality of skin and tissue in a gastric bypass patient is different in healthy normal-weight patients. Their tissue is permanently damaged from being stretched to such an extreme and has lost its ability to maintain tightness or tone.

Factors that determine the degree of redundancy include:

Age: Probably the most important factor in determining how much excess loose skin patients will have following weight loss it is now evident that younger patients tend to have less skin excess possibly due to better tone and skin elasticity.

Degree of MWL: The actual amount of weight loss seems to be a good predictor of the extent of skin and soft tissue excess. Losing 200 pounds following bariatric surgery results in more skin excess than a 100-pound loss.

Inherent tissue type and elasticity: Factors that adversely affect skin tone and elasticity, such as sun-exposure, smoking, co-morbid conditions, lean body mass, muscle tone, especially in the abdomen and buttocks directly impact the amount and extent of tissue excess.

Body contouring in patients who have MWL require surgeons to address the entire body circumferentially and not just one or two specific areas, as is the case with body contouring in more normal-weight patients. Plastic surgeons must re-contour both the entire upper and lower body trunks. Due to the specific nature of the treatment and the careful attention that each procedure needs, patients must be guided to choose a plastic surgeon that has the training and experience in working with post-bariatric patients to ensure a successful outcome.

Six important basic surgical principles frame postbariatric re-contouring:

1 *Realistic goals:* For a successful outcome, this remains the single most important factor for ensuring patient satisfaction. More relevant than in cosmetic surgery in non-MWL patients, the postbariatric surgery patients require a detailed discussion of their problems, an in-depth understanding of the procedures and their limitations. This open discussion using visual aids if necessary (and occasionally patient-support groups) helps in alleviating the inherent fear of undergoing plastic surgery and re-directs unrealistic goals patient might have.

2 *Timing:* Broadly, the re-contouring surgery must be undertaken *after* the weight loss has stabilized. Usually, this may take up to 12–18 months following the bariatric surgery and the patients remain at the same weight for at least 4–6 months demonstrating that their degree of weight loss has reached a plateau. However, it is our opinion that patients are best referred to the plastic surgeon *before* their bariatric operation. It is critical for patients who are planning to undergo bariatric surgery to fully realize that they most certainly will need re-contouring after their weight loss and so that they clearly understand that a plastic surgeon is integral to their post-weight-loss treatment. The best time for plastic surgery to be performed is when the weight has stabilized for several months. Some patients are prepared to have surgery when they still have a few pounds to lose. This is not necessarily a contraindication, since: plastic surgery can reinforce the motivation for further weight loss; the operation can remove some weight that would otherwise have been very difficult to lose, even with the most effective procedure or a very strong diet, e.g. an abdominoplasty can, for example, remove 2–3 kg, a bodylift 4–6 kg, a breast reduction 1–2 kg, and liposuction 1–2 kg.

3 *Safety:* Reduction of postoperative morbidities, by carefully planning the operations, staging multiple operations appropriately, and assessing the patients both physically as well as functionally. Where to begin remains a

crucial question. The best operation to perform first is usually selected based upon defining the patient's view of his/her problem areas. Some patients prefer to start with a breast reduction because postoperative care is short, enabling them to return to work rapidly. For others, even if upset by a hanging abdomen, reshaping their face is a priority because of its obviousness. The most common combination of procedures for contouring is liposuction with body lifting. Some recommend the patient completes a central body lift first, which extends all the way around the lower abdomen and back, to lift the outer thighs, the tummy, and the buttock. Following this at 3–6 months postoperation they can return for an arm lift, inner thigh lift, or a breast reduction or lift.

4 *Direct excision* of tissue excess following MWL remains the mainstay of re-contouring surgery. While liposuction is useful in refining *small* contour abnormalities it has a limited use in patients with MWL where there is always a large amount of skin excess that needs to be directly excised. Liposuction, first described by Ilouz in France in 1983, is primarily indicated for treatment of localized fat deposits. The skin tone is primary determinant of success of liposuction recognizing that this method does not deal with poor skin quality. Excision of the excessive skin remains the mainstay in patients with MWL.

5 Optimal placement of the incisions so as to hide them in contour lines (e.g. the lower abdominal crease, the bikini line or the inframammary crease) allows better acceptability of these operations. Further, minimization of scars by accurately planning the operative techniques guarantees a better aesthetic outcome.

6 Re-suspension of remaining tissues to well-defined fascial structures to allow a lasting, durable reconstruction that will require no further revisions. This surgical advancement has yielded superior results and is probably the most important factor that offers a long-standing benefit to the patient. The classic example is that of the lower body lift, wherein the soft tissue and skin is excised and the lower tissue elements are re-suspended to the superficial fascial system allowing a rigid durable fascia to anchor the lower tissues onto [18–23]. This suspension is crucial in preventing time-related ptosis of the tissues thereby providing patients with a longer-lasting improvement.

Combined Abdomen, Thigh *or* Buttocks Lift *or* the Lower Body Lift

The abdomen is the most common problem zone following MWL. Even in slightly obese men and women, truncal deposition of fat especially in the lower

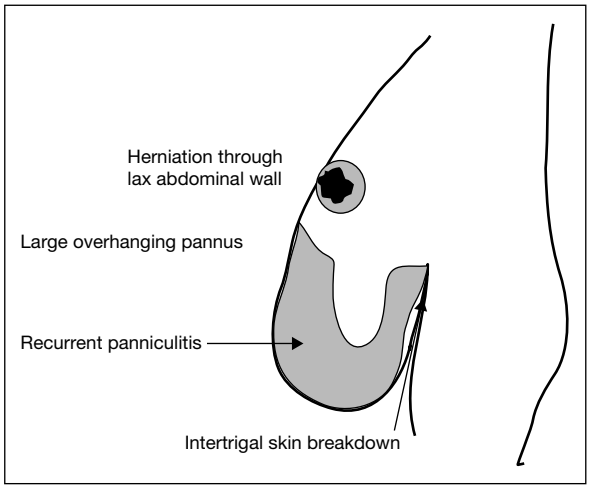

Fig. 2. Physical problems arising from a large overhanging pannus.

abdomen in the Camper's fascial plane is common. Besides aesthetic concerns, MWL precipitates three distinct problems (fig. 2): excessive abdominal skin and soft tissue that drapes over the lower abdomen like an apron; inflammation of the soft tissue of the large overhanging pannus, termed panniculitis; laxity of the abdominal wall musculature that becomes more evident after MWL. Hanging skin and soft tissue creates an acute crease along the lower abdomen that traps sweat and moisture between the skin folds, resulting in a condition called intertriginous dermatitis. The skin becomes irritated, red, and painful with superadded fungal infection and occasionally ulcerates, bleeds or becomes infected. Nonsurgical means of treating this problem include keeping the skin folds dry, but are met with limited success. At best, these methods offer a temporary benefit and usually surgical excision of the tissues is required. Laxity of the abdominal wall musculature can cause herniation that is sometimes difficult to diagnose. Patients could present with sharp, focused pain in a particular area heralding a partial strangulation of a piece of omentum or fat or sometimes with symptoms suggestive of GI obstruction. Careful evaluation of these patients is necessary since these symptoms could arise from herniation as well as post-operative intra-abdominal adhesions. Lastly, some patients continue to develop panniculitis. These present with impressive redness, swelling and pain of a large zone of the abdominal wall, especially the portion that is overhanging. The onset of the inflammation, possible injury and the rapidity of its spread must be carefully documented. Occasionally, the patient can develop a necrotizing infection and may need emergent surgical debridement.

Accurate, timely and complete documentation of these patients' problems remains a key factor in insurance coverage of surgery for excision of the overhanging pannus. Usually, health insurance companies recognize this problem and provide coverage for the surgical removal of the excess skin, a procedure called panniculectomy or an abdominoplasty or tummy tuck. The difference between a panniculectomy and an abdominoplasty is the zones of dissection and whether the abdominal musculature is tightened or not. A panniculectomy simply involves the excision of the overhanging portion of the abdominal skin and soft tissue excess, in a wedge-shaped manner and re-approximating the cut edges. This method is rapid, well-tolerated and provides a marked relief in the patient's symptoms. However, the aesthetic results are not comparable to that offered by an abdominoplasty. An abdominoplasty dissects a larger segment of the abdominal wall and is accompanied with imbricating sutures placed in the rectus fascia that tighten the abdominal wall musculature significantly. The aesthetic goals of an abdominoplasty are to: tighten the lateral trunk and redefine a deep waist concavity; create a central valley between the two rectus abdominus muscles; create a lateral valley lateral to the rectus abdominus and lastly reconstruct a vertically oriented umbilicus. Aesthetically, this method allows for a far superior outcome. Additional liposuction of some of the abdominal zones can add to create a better contouring in some patients. The shortcomings of the conventional abdominoplasty include: over-tightening of the central abdomen with laxity of lateral and inguinal areas; scar depression with adjacent contour deformities; hypertrophic scarring.

One of the main limitations of whether a full abdominoplasty can be safely performed in patients with MWL is the placement of the bariatric surgery scar, usually in the upper abdomen. This incision, commonly performed for most open bariatric surgeries, affects the blood supply to the abdominal flap from the superior aspect. With evolving techniques that perform bariatric operations laparoscopically, these concerns have been alleviated.

Excess skin after weight loss also involves the thighs and buttocks, leading some surgeons to almost exclusively perform a procedure called a lower body lift [16, 24–27]. A lower body lift includes an abdominal, thigh, and buttocks lift done at the same time. The scar is long, but is placed around the waistline and is usually hidden by conventional underclothes or a bikini bottom. The lower body lift was popularized by Lockwood [18–23] and involves a circumferential excision and lifting technique with a 3-dimensional approach to body contouring. It is based on anatomic studies of the underlying superficial fascial system (SFS). The SFS is a tough firm layer of fascia with connections from skin to deeper structures. It is present in most parts of the body and is termed differently based upon the anatomic locations. In the arms, it is called the clavipectoral fascia; breast – suspensory ligaments; abdomen/trunk – Scarpa's

fascia; thighs – colles fascia. The SFS is responsible for supporting the weight of the skin and soft tissues of the body. The position, contour and tone of skin are in turn determined by position and tone of the SFS and its fibrous attachments to underlying musculoskeletal tissues. Besides, the SFS creates 'zones of adherence' that demarcate some key distinctions between anatomic areas, such as the junction between the abdomen and the thighs, etc. The indications for lower body lift include: lower body laxity – skin quality; middle-aged 'relaxation' of tissues; post-pregnancy; MWL. The contraindications to lower body lifting are: nicotine use; significant residual obesity; significant medical problems and co-morbidities that will complicate the postoperative course such as cardiovascular or respiratory compromise; history of deep venous thromboses; psychological factors. Some of the salient features of this procedure include accurate preoperative markings usually with the patient in a standing up position. Careful planning of the incisions is crucial to a successful operation. Usually, the incisions are so marked so that the planned closure line is placed within 'bathing suit lines'. The next step is to accurately judge the amount of excess skin to be removed. Skin to be excised is judged by 'pinching' of excess tissue and the desired postoperative lift simulated during marking maneuvers. Intraoperative positioning of the patient is performed by placing the patient with her/his hips flexed 20–30°; abducted 20–30°. Throughout the procedure, care is taken to padding the pressure zones and maintaining an optimal core body temperature, volume resuscitation, and close monitoring of UOP to ensure adequate flap perfusion. Postoperative care involves: antibiotics, for gram-positive coverage until drains removed, DVT prophylaxis, and inpatient hospital stay of 3–5 days primarily for patient comfort. The major complications of these procedures are: pulmonary embolus $<0.25\%$, major skin necrosis $<3\%$. Minor complications include: hematoma (rare), seroma (3–5%), wound infection, anemia requiring transfusion, parasthesias; standing cones, asymmetry, inadequate lifting; unacceptable scarring.

Breast Augmentation/Breast Lift (Mastopexy)

Breast size and shape often change significantly following MWL. It is important to realize that this affects both genders. Even the natural ageing process (compounded with the effects of gravity) causes the breasts to sag (or develop ptosis) with time. With advancing age the glandular portion (firmer) of the breast is replaced with fat (softer, more pliant). Weight loss will lead to a rapid decrease in the amount of breast tissue. The skin, unable to retract results in sagging breasts, a condition called breast ptosis. Grades of ptosis are well-described and relate to the position of the nipple in relation to the inframammary

fold as well as the positional shift of the glandular tissue in relation to the chest wall [28]. Even without weight loss, breasts become less firm and change shape over time. MWL accentuates this process. Further, women with MWL in their 40s and 50s experience a marked alteration not only in breast size but in shape and position as well. Treatment options for women's breasts following MWL include: breast augmentation alone, in situations where the ptosis is mild and the patients also desire larger fuller breasts; a breast lift (mastopexy) in addition to an implant. The incisions are selected depending upon the patients' preference and the degree of ptosis. In patients with mild ptosis, a circumareolar incision, involving an incision around the areola can be performed. In moderate ptosis, a vertical mastopexy, which involves an incision around the areola and extending from the areola to the base of the breast, is usually necessary. In severe ptosis, an anchor-shaped incision (a vertical incision and yet another horizontal incision in the inframammary fold) may be necessary. In those patients who have an adequate amount of breast tissue, and do not intend to have an augmentation, a breast lift without an implant is effective. The goal of mastopexy is to reduce breast 'sag' and improve breast shape. Risks of the surgery include: altered nipple sensation; altered ability to breastfeed; healing difficulty, and rarely a complete loss of nipple-areolar complex due to poor blood supply.

It is important to recognize that men who have MWL have breast problems similar to women. The terminology and treatment are vastly different. Obese men tend to have large breasts (termed gynecomastia) [29–31]. Even following MWL, some fat and glandular tissues remain in addition to the skin excess. The extent of weight loss in male patients with MWL who develop gynecomastia requiring further surgery depends on their age. In a certain segment of carefully selected patients with gynecomastia, liposuction alone offers an adequate treatment. In most males, however, direct excision of fat and glandular tissue and an ellipse of hanging skin are necessary.

Arm Lift (Brachioplasty)

In female as well as some male patients with MWL, loose skin and soft tissue in the arms is unsightly and hard to conceal. There are three surgical options to improve the appearance of the arms: (1) In patients with good skin tone at the arms, liposuction alone may be successful. (2) A modified brachioplasty (arm lift) can be performed if the amount of excess skin is mild. The surgeon tightens the excess skin of the arm and armpit in the armpit area, leaving a well-concealed scar. A modified brachioplasty may be combined with liposuction. (3) A conventional brachioplasty is usually the best option in patients with significant

excess skin. The goals are to reduce redundant skin and improve arm contour. This procedure involves a scar in the armpit as well as one along the inside of the arm. Most patients will accept the arm scar in exchange for an improved arm contour. A classic brachioplasty may be combined with liposuction. Risks of the procedure include injury to superficial nerves including the antebrachial cutaneous n., brachial cutaneous n., and wide visible scarring.

Face Lift

MWL accelerates as well as accentuates the process of facial aging. With MWL, the fatty layer beneath the skin attenuates at a faster rate; laugh lines and other facial wrinkles or rhytids become more pronounced. As opposed to the normal aging process, in patients with MWL there is significantly visible excess skin along the cervical area due to the fact that in obese patients the neck is repository for fat. Several advancements in face lift techniques as well as a better understanding of the aging process have enabled the development of more effective surgical methods to rejuvenate the face and neck. Scars are shorter, better hidden; morbidity is reduced as well as the postoperative recovery is shorter. As plastic surgeons, it is important to customize each procedure to the individual needs to optimize the cosmetic result. A face lift, which almost always incorporates a neck lift, seeks to obliterate the deeper facial rhytids of the face as well as the excess fat and skin of the neck. A face lift usually involves an incision beginning in the scalp above the ear, continuing immediately in front of the ear and extending around and behind the ear and just inside the hairline below the ear. The overlying skin is elevated, and the excess is removed. The superficial fascial layer just under the skin is plicated and tightened. Excess tissue in the neck is removed by a neck lift, termed cervicoplasty. The goal is to reduce/eliminate redundant skin of lower face and neck. Potential risks of both the face and neck lifts include facial nerve injury, hematoma and visible scarring or delayed (especially smokers).

Conclusions

Bariatric surgery isn't just a commitment to weight loss. It often requires an additional 2 years of body contouring surgeries to help the patient's skin fit his or her new body. The results in terms of increased function in society and dramatic improvement in body aesthetics and image argue for integrating plastic surgery into the comprehensive treatment plan for the bariatric patient.

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Psychosocial Aspects of Obesity

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Abstract

Obese patients have many physical limitations and much psychiatric burden to overcome. Several studies have shown that the prevalence of psychiatric morbidity in the obese is similar to those with normal weight. However, in obese patients seeking treatment there is an increased prevalence (40–60%) of psychiatric morbidity, most commonly depression. It is difficult to separate the effects of depression on obesity and, on the contrary, the neuroendocrine changes associated with stress and depression may cause metabolic changes that predispose and perpetuate obesity. The stigma associated with obesity causes bullying in school as well as childhood psychiatric morbidity. Prejudice is not limited to the general public but exists among health professionals too. This chapter discusses the treatment of depression in obesity and the psychiatric evaluation of the pre-bariatric surgery patient. Education of society, starting with schools and including healthcare professionals will reduce bias and stigma as well as assist this vulnerable group of patients to seek help for their obesity and the many problems that come with it. Given that by the year 2025 obesity will be the world's number one health problem with the US leading the way, it is very important that we pursue preventive measures as well as encourage research for treatments of obesity.

The increasing prevalence of obesity in the USA and its medical, social, psychological and economic implications has made it a national health crisis. Obesity is predicted to be the number one health problem globally by the year 2025. Although men have higher rates of overweight, women tend to have higher rates of obesity. For both, obesity poses a major health risk for diabetes, cardiovascular disease, hypertension and certain forms of cancer. Obesity is defined as a condition of excess body fat and is associated with a large number of debilitating and life threatening disorders. It is conventionally measured as a Body Mass Index. The BMI charts classify patient's weight as: underweight <20, healthy 20–25, overweight 25–30, obese 30–40, and superobese 40 and above, signifying increased risk of medical co-morbidities. Studies indicate that

BMI varies for different races [1]. Mortality and Morbidity vary with the distribution of body fat, with the highest risk being linked to excess abdominal fat also known as 'central obesity'. A study by Gopalan revealed that nearly 20% of adults who were not overtly obese still had central obesity, putting them at a greater risk of developing non-insulin-dependent diabetes (NIDDM), hypertension and coronary heart disease (CHD) [2].

In this chapter, we will review the psychological aspects of obesity and its treatment.

Global Epidemic of Obesity

With the use of WHO standardized classification of obesity the following data about the worldwide prevalence of obesity was obtained [3]. The prevalence of obesity ranges between <5% in rural China to 75% of adults in Samoa. 22 million children under 5 years of age are overweight. Many countries have experienced a startling increase in obesity over the last 10–20 years, and based on current trends predictions have been made that the level of obesity would be 40–45% in the USA by 2025, 30–44% in Australia, England and Mauritius, and 20% in Brazil. The prevalence of obesity varies between socioeconomic groups as well as between developed versus 'developing countries'. The higher prevalence of obesity in lower socioeconomic groups is thought to be a measure of health awareness and education as well as cost of 'health/diet foods' or joining a gym. The higher educated have the financial stability to maintain their healthy weight. There also exits a difference in obesity prevalence in developing versus developed countries. In developed countries, lower socioeconomic groups have a higher rate of obesity; however, in developing countries, an increased prevalence of obesity is seen in higher socioeconomic groups. This could be explained by the lower cost of fast foods, higher costs of health clubs and possibly a more sedentary life style in developed countries. In developing countries, the lower socioeconomic groups have to be more physically active, e.g. walk or take public transportation, their diets also tend to be low calorie and they have limited access to fast foods.

Etiology of Obesity

The etiology of obesity is multifactorial and usually an interaction of genetic predisposition, environment and its effect on metabolism. The current environment is blamed heavily for the increasing obesity, because it is argued that the 'gene pool' has remained relatively stable, whereas the environment has

changed rapidly with increased intake of processed foods and more sedentary life-styles. Metabolic factors causing obesity, identified as being under substantial genetic influence, are low resting metabolic rate for a given body size and composition, a high respiratory quotient indicating low fat oxidation and a low spontaneous physical activity. Important environmental factors include low levels of physical activity, increased inactivity and a high fat diet. Obesity exhibits both genetic and familial association suggesting an individual susceptibility that interacts with adverse environment to cause weight gain.

Physiology of eating behaviors and obesity is discussed in detail in the chapter by Aja and Moran [this vol., pp. 1–23]; it is mentioned here briefly in context with depression and stress. The discovery of leptin receptors and complex neuropeptidergic pathways that control energy balance have shown that body fat content is partly under non-conscious homeostatic control. Recent studies suggest that several areas of the brain that may have connections with the hypothalamus are involved in the conscious hedonic control of eating. They establish cognitive and emotional processes that reinforce the properties of food as a stimulus for pleasure and reward [4]. While it is difficult to separate the need to eat from the pleasure of eating, the reward value of food often overrides the physiological signals of hunger and satiety [5]. Dopamine is thought to mediate the anticipation of reward, and shows higher activity in limbic and paralimbic structures in response to the sight of food. The sight of food also has been shown to increase cerebral blood flow in the right parietal and temporal cortex in obese women, but not in women of normal weight [6].

Studies also show that the hypothalamic-pituitary-adrenal axis with its response to stress and increased cortisol secretion can be related to the development of obesity as well as perpetuating obesity in a predisposed individual. It is believed that glucocorticoid exposure is followed by increased food intake and ‘leptin-resistant obesity’. Recent animal experiments have shown that corticosteroids induce leptin secretion and a condition of ‘leptin resistance’ is induced by glucocorticoid excess. Human obesity is also characterized by elevated leptin levels, from ‘leptin resistance’ [7].

Neuroimaging studies have established that a meal directly inhibits hypothalamic neuronal activity, which may be elevated in hunger. In obese individuals, the decrease in hypothalamic activity following a meal is significantly reduced compared with lean individuals [8].

Elevated cortisol, especially with secondary inhibition of growth hormone and sex steroids, causes accumulation of fat in the visceral adipose tissues (central obesity) as well as metabolic disturbances; also known as the ‘metabolic syndrome’ [9].

Depression, a hypercortisolemic condition, has been associated with an increased risk of developing cardiovascular disease, type 2 diabetes mellitus as

well as somatic symptoms characterizing the metabolic syndrome. Recent studies have shown that these metabolic abnormalities have improved in men with depressive symptoms that have been treated with serotonin reuptake inhibitors [9].

Although the cause of obesity is multifactorial, the attitudes toward it characterize it as a measure of 'self-control', leading to societal bias.

Psychiatric Illness and Obesity

Several studies have shown that the prevalence of psychiatric morbidity in the obese is similar to those with normal weight. However, in obese patients seeking treatment there is an increased prevalence (40–60%) of psychiatric morbidity, most commonly depression [10]. Most patients are depressed about the negative effects of obesity in every aspect of their life: health, social life, finance, mobility and functioning. These patients are also on medications that can sometimes cause depression, e.g. atenolol. Conversely, medications that patients may take for their psychiatric symptoms can also result in weight gain, e.g. paroxetine and olanzapine cause weight gain.

Psychological status of an individual depends on several factors including genetic, environment, personality and life experiences. Obese patients have the added burden of weight and its manifold effects on their lives. A vicious cycle often exists where the obese patient indulges in comfort/emotional eating and this results in further weight gain. As discussed above, it is difficult to separate the effects of depression on obesity and the reverse, the neuroendocrine changes associated with stress and depression may cause metabolic changes that predispose and perpetuate obesity.

Depression and emotional symptoms can isolate the patient resulting in their not seeking health care, which in turn may affect a health outcome like heart disease. The increased medical morbidity as well as limitations in mobility caused by obesity has a direct impact on the patient psychologically. Many patients report 'social anxiety', they are embarrassed to go out because they may not 'fit' into a chair in a restaurant or airplane. Their self-esteem is reduced and they often have issues with their body image which can persist despite weight loss. The effect on their social life leaves them isolated and vulnerable.

Comorbid psychiatric illness usually in the form of depression often stems from reduced functionality and increased medical problems. In a recent study, almost two thirds of patients presenting for bariatric surgery had a psychiatric diagnosis, with major depression being the most common and less than half of all patients were in some type of psychiatric treatment. Additional dietary and psychiatric counseling was recommended for a third of the patients prior to surgery and only 3% were not recommended for surgery [11].

Recent studies have shown that excess weight in females is associated with an increased risk of major depression, substance abuse and suicidal ideations (surprisingly in males the inverse was found, excess weight was associated with a reduced risk of depressions and suicidality) [12]. Several studies have reported impaired quality of life in obese individuals.

An unpublished study by Vaida on 'Body image and sexual functioning in obese patients presenting for gastric bypass surgery' in 247 preoperatively bariatric surgery patients, using well-validated scales like the DISF (Derogatis Inventory of Sexual Functioning), MBSRQ (multidimensional body self relations questionnaire) and the NEO Personality Inventory, showed that both men and women scored almost 2 SDs below norms for sexual functioning and for body image. Women showed a positive correlation between weight and the domain of 'sexual cognition and fantasy'. Heavier women had higher scores in the domains of fantasy. Women who perceived themselves as overweight did poorly on drive and relationships and those who valued fitness and were actively involved in exercise had higher scores on arousal, behavior, orgasm and drive.

A significant number of patients experience body image difficulties postoperatively, as the weight loss with bariatric surgery is significant and relatively quick. Obese patients with difficulties with body image preoperatively tend to sustain this postoperatively and patients who tend to view themselves as attractive maintain this postoperatively. It is therefore important to identify vulnerable individuals preoperatively, and direct specific measures to optimize outcomes and improve quality of life.

Eating Disorders

Eating disorders are addressed in detail in the next chapter. The reason to briefly mention them here is that binge eating is a reliable marker for symptoms of depression. Multiple studies have shown that mood is essentially normal in obese individuals who do not suffer from binge eating disorder (BED), while those with BED report higher levels of depression, anxiety as well as obsessive behavior [13]. For details on treatment of BED please refer to the chapter by Vaidya [this vol., pp. 86–93].

Stigma

Stunkard described obesity as 'the last remaining socially acceptable form of prejudice'. The stigma associated with obesity causes bullying in school as well as childhood psychiatric morbidity. Prejudice is not limited to the general

public but exists among health professionals too [14]. Negative attitudes amongst health professionals can seriously impede patients from seeking help for their ailments, thereby worsening their problems as well as increasing bias and distance between themselves and healthcare. Stigma/bias associated with obesity is as old as obesity itself [15]. Many recent studies have demonstrated the existence of significant bias against obese patients in all aspects of life, i.e. school, employment, relationships and healthcare. The tendency of healthcare workers to be biased can have a far-reaching negative impact on the obese patients and their multiple medical problems. The bias tends to exist at an early age when children attribute negative elements to obese individuals [16]. It exists across cultures and Crandall et al. [17] compared attribution toward obese people in 6 different countries. They found that 'anti-fat' attitudes were best predicted by views that people were responsible for life outcomes along with cultural values that hold negative views against 'fatness'. Countries like Australia, Poland and the US ranked high on individuality had greater 'anti-fat' attitudes than those that ranked low on individuality like India, Turkey and Venezuela. Even obese patients had biases against other obese patients. The increased prevalence of obesity has done nothing to reduce the stigma associated with it.

Personality

While there is consensus that no particular personality is associated with obesity, there is a subgroup of patients who are successful in maintaining weight loss who have certain personality attributes [18]. Patients who were successful in maintaining weight loss demonstrated:

- Greater initial weight loss
- Reached a self-determined realistic goal
- A physically active lifestyle
- A regular meal rhythm including breakfast and healthier eating
- Control of overeating and self-monitoring of behavior

Weight maintenance was further associated with internal motivation to lose weight, social support, better coping strategies and ability to handle life stress. Patients with self-efficacy, autonomy, assuming responsibility in life, and overall more psychological stability were able to keep their weight down.

Treatment of Depression in Obese Patients

Depression is frequently a comorbid condition in patients seeking treatment for obesity. There also seems to be a slight increase in depressive

symptoms soon after bariatric surgery. While several patients report that their depression resolves spontaneously some need medication and support through the postoperative period. Medications work best with psychotherapy, support and weight loss programs.

Medications

Once a patient is diagnosed as having a depressive or anxiety disorder, an antidepressant medication should be considered. The choice is based on the patient's symptoms as well as prior history of medications as well as response. There is a potential for increased gastrointestinal side effects with most SSRIS; however, if the patient has been on them before with a good response, it can be initiated at a small dose and increased as tolerated/needed. Paroxetine has been reported to cause weight gain and hence should be avoided. Many patients are lethargic and need an 'energizing antidepressant'. Venlafexine, usually extended release starting at 37.5 mg for 7 days increasing to 75 mg daily, helps reduce symptoms. It blocks the reuptake of norepinephrine and serotonin. Studies have shown that venlafaxine effectively reduces binge-eating frequency and severity as well as mood in obese patients [19]. It is important to let the patient know that most antidepressants take 2–3 weeks to show an effect. The medication can be increased gradually as needed to optimal tolerated dose. Venlafexine has also been reported to have the least propensity for drug-drug interaction which makes it the ideal choice as many of the patients are on multiple medications for their other medical problems. A potential side effect of venlafexine is hypertension. It is therefore prudent to monitor blood pressure at least until the patient is stable on therapy. After bariatric surgery patients often need the antidepressant dose lowered, less often the dose may need to be increased due to possible erratic absorption during the postoperative period. The importance of follow-up and dose adjustments cannot be understated.

Psychotherapy

Depressive symptoms in obesity affect many aspects of the patient's life and cannot be treated with medication alone. Most patients require some form of psychotherapy and support.

Both group therapy as well as individual therapy have been shown to complement medications [20]. Given that obese patients tend to have issues with intimacy, body image and emotional eating, group therapy specifically focused on these issues should address patient needs adequately.

Bariatric surgery patients have a host of issues unique to them. Many patients 'grieve' for their 'friend' the food, and have to be helped in coming to terms with an altered lifestyle. They tend to eat in response to stress, and need help finding alternate coping mechanisms. Psychotherapy helps patients by

giving them tools to employ for anxiety or stress, which ordinarily would have caused them to eat. Relaxation techniques, interpersonal therapy and cognitive behavior therapy have been found to be especially helpful with medication [21].

Treatment of Obesity

Obesity can be treated by nonsurgical methods, namely diet, exercise and medication. These have been further discussed in detail in the chapters by Greenwald and Sidhaye [this vol., pp. 24–41, 42–52, respectively]. While they are noninvasive they tend to have poorer outcomes in the long term. Surgical methods employed now are optimally revised and have been shown to be the treatment of choice for morbidly obese patients, who are not successful in maintaining weight loss, those with multiple medical problems, reduced life expectancy and poor quality of life [22].

The details of surgical methods are detailed in the chapter by Schweitzer et al. [this vol., pp. 53–60].

Psychiatric Evaluation of Patients Prior to Bariatric Surgery

At Johns Hopkins all patients seeking bariatric surgery have to have a preoperative psychiatric evaluation. The patients are usually highly motivated to undergo the surgery and are eager to impress the psychiatrist of their ability to cope with the postoperative issues. It is helpful to get a battery of tests to assist in identifying the specific vulnerabilities of the patients. The Massachusetts General Hospital has published a presurgical psychiatric interview for patients presenting for bariatric surgery [23].

The interview with the patient is complemented by speaking with their family, especially in younger patients, to assess the degree of support available.

It is best to evaluate the patient after he/she has seen the surgeon to ensure that they have an understanding of the risks and benefits of the surgery, as it pertains to them.

Psychiatric evaluation can identify psychological and/or social risk factors, as well as make recommendations to address these factors to ensure the best possible outcome. The surgery itself has a broad range of effects on the patient. Apart from a whole new life style after surgery, the patient has to deal with initial dietary restriction, permanent change in the patient's eating habits, altered body sensations, shifting body image, and changing cognition and feeding. In addition, they may have significant changes in relationships that may result in

stress and psychological symptoms. Bariatric surgery not only reconfigures the patient's stomach but also affects the patient psychologically.

It is therefore essential for patients to have a secure identity and sound psychological resources, resiliency, effective coping strategies and a willingness to access support.

Psychiatric evaluation should include the following:

Behavior

- Previous weight management efforts
- Eating and dietary styles: evidence of disordered eating especially binging
- Physical activity and exercise
- Substance abuse and legal history
- Health-related risk-taking behavior such as noncompliance, compulsive behaviors

Cognitive and emotional

- Patients should have the intellectual reasoning to understand the surgical procedure and risks, with behavioral changes required to manage the surgically altered stomach
- Coping skills for positive as well as negative stressors
- Psychopathology: psychiatric symptoms, depression/anxiety/suicidality, previous history of psychiatric illness, compliance with treatment as well as risk of relapse immediate and long term. Treatment history from previous providers. One should attempt to speak to the current provider of treatment with the patient's permission
- Potential medication issues postoperatively, poor absorption, effect on weight

Developmental history

- Childhood sexual abuse, any evidence of deliberate self-harm
- Family history of psychiatric illness/suicide/substance abuse/obesity
- Life events and adjustment to them can shed light on patients resources and coping skills
- Quality of social relationships
- Current life situation: stressors/utilization of social support, motivation and expectations

Psychiatric testing and scales:

The list below reflects areas to be screened, with examples of tools that we have found helpful. Test data may support/challenge the clinical impression and help screen for and quantitate the following:

1 Depression: BDI/HAMD, etc.
2 Personality: NEO PI (self and rater)
3 Body image: MBSRQ

4 Sexual function: DISF
5 Quality of life: BAROS [24]
6 Binge eating: BES

The evaluation should state clearly if the psychiatrist/psychologist believes the patient is appropriate for surgery or not and the reasons. It should include diagnostic and therapeutic recommendations for patient's specific issues. The patient should follow-up 6 months to a year after surgery to ensure appropriate management of symptoms.

For patients with a history of BED, a longer follow-up is recommended as these patients tend to return to their behaviors usually after a year and a half after the operation, resulting in regain of some weight. Table 1 lists some of the possible problems encountered at interview with a rough guide to recommendations. *It is important that each patient's strengths and weakness be analyzed individually; the table serves as a guide only.* If the patient needs psychiatric treatment it is important to identify a goal/period after which the patient is reassessed for surgery, usually about 6–12 months engaged in psychiatric treatment. Certain criteria increase the risk of postoperative noncompliance such as substance abuse, a history of noncompliance with recommendations in the past, suicidality, pychosis, impulsive behaviors, recent history of deliberate self-harm, unrealistic expectations (table 2). Patients who eat in response to emotions such as depression/anxiety also will tend to repeat the behaviors after the operation. They benefit from CBT and medications to treat their psychiatric symptoms.

Bariatric surgery is a life-changing event that has a great impact on the patient physically as well as mentally. Most patients tend to lose 50–70% of their excess weight 6–12 months after the opeation resulting in changes in every aspect of their lives.

Exercise and smoking have been shown to be closely linked to surgical outcome. Exercise frequency has been shown to be inversely related to the number of medical problems. Presurgical smoking frequency was inversely correlated to 'proximity to goal weight'. Satisfaction with the surgery was positively correlated with exercise frequency but negatively correlated with smoking frequency [25].

While the determination of these patients' ability to deal with the surgery and its lifelong restrictions is difficult it should be based on the patient's understanding of the procedure, his/her other strengths, coping, personality, social support and motivation. Psychological factors have not been found to predict weight loss or drop out from treatment, nor are they a contraindication for bariatric surgery. However, they can reduce the quality of life and treatment of the same can optimize outcomes of surgery [26].

Table 1. Risk factors in the prebariatric psychiatric evaluation

Problems at interview	Recommendations
Psychiatric illness unstable	treatment and revaluate 6 months to a year after stable and engaged in treatment
Substance abuse currently active	treatment of substance abuse and revaluate after 1–2 years clean and engaged in recovery
Risky impulsive behaviors	psychotherapy and medication and revaluate 6–12 months
BED/eating disorder NOS	referral to special ED clinics; CBT and revaluate 6–12 months engaged in treatment; frequent postoperative follow-up that lasts longer than 3–4 years postoperation
Reduced social support	assist patient in identifying needs and support groups; involve social services and case management

Table 2. Patient traits affecting weight control

Positive traits that help maintain weight loss	Negative traits that associated with poor weight control (postoperative noncompliance)
1. Internal motivation to lose weight	1. Current psychiatric instability, or substance abuse, suicidality/psychosis
2. Social support	2. History of noncompliance with recommendations in the past
3. Better coping strategies ability to handle life stress	3. Impulsive behaviors
4. Patients with self efficacy, autonomy, assuming responsibility in life	4. Recent history of deliberate self-harm
5. A regular meal rhythm	5. Unrealistic expectations of weight loss treatment
6. Physically active life style	
7. Ability to seek help when needed	

Comorbid psychiatric illness should not disqualify patients from surgical treatments; in fact, some studies have shown that patients with BED benefit greatly from the surgery with greater satisfaction among patients. It has also been shown that their psychiatric illness was unaffected by surgery.

Conclusion

Obese patients have many physical limitations and much psychiatric burden to overcome. Education of society, starting with schools and including healthcare professionals will reduce bias and stigma as well as assist this

vulnerable group of patients to seek help for their obesity and the many problems that come with it. Given that by 2025 obesity will be the world's number one health problem with the US leading the way. It is very important that we pursue preventive measures as well as encourage research for treatments of obesity.

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Cognitive Behavior Therapy of Binge Eating Disorder

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Abstract

Binge eating disorder (BED) is characterized by recurrent episodes of uncontrollable eating, even when not hungry, until uncomfortably full, occurring at least twice a week for a 6-month period. This is differentiated from bulimia nervosa (BN) by the lack of compensatory mechanisms such as purging/laxative abuse. There are significantly higher levels of psychiatric symptoms in patients with BED as compared to those without BED. Furthermore, depressive symptomatology may increase the patient's vulnerability to binge eating as well as to relapse after treatment. Grazing is defined as eating small amounts of food continuously. BED in the pre-bariatric patient can manifest as 'grazing' about 2 years post-bariatric surgery. Treatment should be directed at eating behavior, associated psychopathology, weight and psychiatric symptoms. Cognitive behavior therapy is based on changing the patient's erroneous ways of thinking about themselves, the world and how others perceive them. This includes a focus on normalizing food intake as well as challenging dysfunctional thinking, identifying feelings, and developing non-food coping skills. It increases a sense of control and therefore helps the patient adhere to behavior change strategy, as well as improving mood and reducing associated psychopathology. Interpersonal therapy is based on the relationship between negative mood low self-esteem traumatic life events, interpersonal functioning and the patient's eating behavior. The rationale being that eating represents maladaptive coping with underlying difficulties. While psychotherapy either CBT or IPT leads to decrease in disordered eating behaviors and improved psychiatric symptoms, it has little effect on weight hence; its benefit is optimal when used in conjunction with bariatric surgery.

Binge eating was first described by Stunkard [1] in 1959 as a behavior seen in certain obese individuals that consisted of uncontrolled consumption of objectively large amounts of food. Binge eating disorder (BED) was included in the DSM IV as a proposed diagnostic category for further study and as an example for an 'eating disorder not otherwise specified' (table 1) [2]. Although it is not

Table 1. Diagnostic criteria for binge eating disorder

1	Recurrent episodes of binge eating characterized by the following: • Eating an amount of food that is larger than most people would eat, in the same circumstances, in a discrete period of time • Lack of control during the episodes, feeling that one cannot stop eating or control how much one is eating
2	Binge eating episodes are associated with at least three of the following indicators of loss of control • Eating more rapidly than usual • Eating until uncomfortably full • Eating large amounts of food when not hungry • Eating alone because one is embarrassed about how much one is eating • Feeling disgusted with oneself, or guilty about the binge or depressed
3	Marked distress over binge eating
4	The binge eating occurs at least 2 days a week for a 6-month period
5	The binge eating is not associated with the regular use of in appropriate compensatory behaviors (e.g. purging fasting, excessive exercise) and does not exclusively occur during the course of anorexia nervosa or bulimia nervosa

limited to obese individuals, BED is most common in this group. Those who seek help, usually do so for being overweight rather than for the binge eating.

Prevalence of BED has been estimated to be about 2–5% in a community survey, 30–40% in treatment seeking obese patients and probably higher in 'super obese' patients. Individuals in Overeaters Anonymous had a prevalence of 70% for BED [3]. BED is more equal in gender ratio than bulimia nervosa (BN) and has a similar prevalence among racial groups.

BED is characterized by:

- Recurrent episodes of eating uncontrollably indicated by
  1 eating more rapidly than usual
  2 eating until feeling uncomfortably full
  3 eating large amounts of food when not hungry
  4 eating alone
  5 no planned mealtimes
  6 eating in response to emotions
  7 guilt about overeating
- Binge eating occurring at least twice a week for a 6-month period.

This is differentiated from BN by the lack of compensatory mechanisms such as purging/laxative abuse. Bulimics have a greater size of a 'binge meal' as compared to patients with BED. Although patients with BN consume fewer

calories than patients with BED, they tend to have a more disturbed pattern of eating [4]. BED is associated with increased psychopathology including depression and personality disorders [5]. There are thought to be subtypes of BED; those driven by psychological factors versus those driven by physiological factors the differentiation being important tool to help focus treatment strategies [6]. Psychologically driven binge eating refers to patients eating in response to stress or depression. Physiologically driven binge eating can result from semi starvation and restricted eating which can lead to preoccupation with food. If eating is initiated in a state of intense hunger reactive overeating can occur, or if restrained eating is disrupted via disinhibition [7].

Another syndrome has been identified as causing disturbed eating patterns, night eating syndrome. Night eating syndrome is defined as skipping breakfast more than four days a week, consuming more than 50% of calories after 7 p.m. and difficulty falling asleep or staying asleep more than 4 days a week. The prevalence of NES in pre-bariatric patients is reported to be as high as 26% and about 27%, 32 months postoperation [8].

Etiology

As with most eating disorders, the cause of BED is multifactorial including genetic, social and psychological influences. Overeating represents lack of interoceptive awareness and inability to discern internal cues. Studies have shown no evidence that binge eating results from dietary restraint in obese patients [9]. About half the patients with BED report that they first started to binge in the absence of dieting. Disinhibition as opposed to dieting seems to precipitate binge eating in many obese subjects [10]. Negative emotional states such as frustration, anger depression and anxiety, social situations, and type of meal have been known to trigger an episode of binging [11]. There are few studies on the physiological differences between obese patients with and without binge eating, with any evidence to suggest that obese patients with BED had more medical consequences of obesity than those without BED [12].

There are significantly higher levels of psychiatric symptoms in patients with BED as compared to those without BED [13]. Furthermore, depressive symptomatology may increase the patient's vulnerability to binge eating as well as to relapse after treatment.

BED is thought to be associated with exposure to risk factors for psychiatric disorders like parental depression, childhood sexual or physical abuse, negative self evaluation, and pregnancy before onset [14]. They were also associated with exposure to risk factors for obesity, childhood obesity, and critical comments by family about shape, weight or eating. Other antecedents of binge eating are low alertness, feelings of low control over eating and craving sweets [15].

Grazing is a condition that may arise from 'boredom, mindlessness' or be compulsive or emotional in nature. It is defined as eating small amounts of food continuously. BED in the pre-bariatric patient can manifest as 'grazing' about 2 years post-bariatric surgery. The patient learns to 'eat around the surgery' resulting is weight regain in these patients [16]. It has been reported that some patients, feel a loss of control over eating as early as 6 months post-bariatric surgery [17]. Body image dissatisfaction is more pronounced in obese patients with BED than in obese non-binge eaters [18].

Treatment

Successful treatment of binge eating may not affect much weight loss, however it does tend to stabilize weight in comparison to the upward weight trend in patients who continue to binge [19]. Some hold the view that treatment should be directed at disordered eating and associated psychopathology first and only after control of binge eating should additional weight loss measures be considered [20]. However, several studies have shown that weight loss treatments including bariatric surgery do not exacerbate binge eating. In fact patients with the most severe binge eating behavior showed the most improvement especially in the short term [21]. Given that obesity is frequently present in patients with BED and raises the patient's medical morbidity, it is important to consider interventions that also produce weight loss.

Treatment should be directed at eating behavior, associated psychopathology, weight and psychiatric symptoms. Several studies report success with pharmacological and psychological interventions [22, 23]. Medications used successfully to treat BED include selective serotonin reuptake inhibitors, anticonvulsants like topiramate, zionasmide as well as sibutramine [24].

Treatments should be appropriately modified to better fit a post-bariatric surgery patient. Traditionally, eating disorder patients are encouraged to have 'three fixed meals'. Bariatric surgery patients have to eat small frequent meals. Their dietary restrictions and changes need to be reflected in a modified program to fit their needs. Bariatric surgery patients also tend to be, more preoccupied with food postoperatively; this seems to be more of an attempt to comply with treatment and usually reduces as their habits get more routine.

Cognitive Behavior Therapy

Cognitive behavior therapy (CBT) is based on changing the patient's erroneous ways of thinking about themselves, the world and how others perceive them. It is thought that patient's disordered 'schema' of thoughts perpetuates

Table 2. Phases of CBT

Phase I
• Establish therapeutic relationship
• Implement psychoeducational materials
• Self-monitoring and record keeping of eating behaviors
Phase II
• Identifying maladaptive cognitions regarding eating
• Using cognitive restructuring techniques
• Identifying triggers for binge eating
• Continued focus on normalizing eating pattern
• Address emotional changes post-bariatric surgery patients with special attention to body image, relationships
Phase III
• Maintenance of change
• Identify high risk situations
• Develop relapse plan

self defeating behaviors and causes depression, anxiety and eating disorders. It has been well studied and shown to be highly effective for treatment and prophylaxis of depressive and anxiety disorders [25]. It was modified for treatment of BN and more recently for BED [26]. This includes a focus on normalizing food intake as well as challenging dysfunctional thinking, identifying feelings, and developing non-food coping skills. It increases a sense of control and therefore helps the patient adhere to behavior change strategy, as well as improving mood and reducing associated psychopathology [27].

The process can be divided into several phases, the specific tasks and issues arising at each phase being woven around a constant theme (table 2).

Phase I

Involves establishment of a collaborative therapeutic relationship while focusing on educating the patient about the nature of binge eating and factors thought to maintain the problem. Specific behavioral strategies involving food diaries for self-monitoring of food intake, helps patient to identify the disordered eating, while working towards a normalization and structured or regular pattern of eating.

For post-bariatric surgery patients, the focus is on the dietary adjustments, loss of their 'friend' food, their changed relationship to food, changes in their bodies and their relationships with others.

Phase II

Integrates cognitive procedures where patients learn to identify and challenge maladaptive thoughts regarding eating and weight/shape. In this phase the patient identifies thoughts that are triggers for binge eating. The patient is

encouraged to continue normalizing eating patterns with the use of cognitive restructuring techniques.

For the post-bariatric surgery patient special attention is paid to body image and relationships. The rapid loss of weight postoperatively can result in disruption of the 'homeostasis' of the relationship with their partner and result in relationship difficulties [28].

Phase III

Focuses on maintenance of change and relapse prevention, by identifying high risk situations and developing a relapse plan.

The group usually works well with 6–8 patients meeting weekly and can last for 12 weeks with the ability for patient to return if needed as well as additional individual therapy as needed.

Once an eating pattern is established preoperatively (the severity determines treatment) the patient should be referred for CBT to reduce behaviors. Patients eating in response to mood such as depression/anxiety should be taught alternative ways like relaxation to deal with the symptoms/or started on antidepressant/anxiolytic medications. CBT for these patients helps reduce symptoms and improves quality of life as well as self esteem. When the patient is engaged and compliant and behaviors have reduced or are considered under control, the patient may be reassessed for bariatric surgery. Binge eating behavior prior to bariatric surgery can result in 'grazing' about 2 years postoperatively [16]. While BED is not a contraindication to bariatric surgery, it is very important that such a patient have close and extended postoperative surgical/nutritional and psychiatric follow-up.

Interpersonal Therapy

This was initially developed to treat depression, later modified for the treatment of BN and most recently for the treatment of BED. Interpersonal therapy does not focus on eating behavior, but on relational factors associated with the onset and maintenance of binge eating [27]. It is based on the relationship between negative mood low self-esteem traumatic life events, interpersonal functioning and the patient's eating behavior. The rationale being that eating represents maladaptive coping with underlying difficulties.

Techniques

It is a short-term time limited therapy.

Phases of treatment include clarification of emotional states, improvement in interpersonal communications. Reassurance testing of perceptions and performance through interpersonal control.

Conclusion

Cognitive behavior therapy has clear positive effects on behavioral and psychological features. Wilfley et al. [27] and Agras [29], in their studies, suggest that patients who are in remission from binge eating achieve greater weight loss than those who are not in remission. It has been suggested that adding exercise to CBT as well as extending the duration of treatment improves outcomes and reduces binge eating [30].

Given that there are identified antecedents to binge eating, applying CBT or IPT to modify these areas benefits the patient. The use of antidepressant/anxiolytic medication as an adjunct to psychotherapy improves quality of life as well outcomes. While psychotherapy, either CBT or IPT, leads to a decrease in disordered eating behaviors and improved psychiatric symptoms, it has little effect on weight; hence, its benefit is optimal when used in conjunction with bariatric surgery.

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