CONTEMPORARY ENDOCRINOLOGY™

# Type 2 Diabetes Mellitus

## *An Evidence-Based Approach to Practical Management*

Edited by

**Mark N. Feinglos, MD**
**M. Angelyn Bethel, MD**

Humana Press

# Type 2 Diabetes Mellitus

# Contemporary Endocrinology

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# Preface

As the global epidemic of diabetes continues to expand, the prevalence of type 2 diabetes is predicted to double in the next 20 years. Continued population growth, increasing age, and worldwide globalization leading to changes in diet and patterns of physical inactivity have resulted in staggering numbers of individuals affected by the disease. A haphazard approach to treatment for a problem of this magnitude could easily overburden the healthcare system, particularly in areas of the world with limited resources. The development of a rational approach to therapy should be based on data derived from the strongest level of clinical evidence available, with the goal of balancing the risks, benefits, and cost of care.

In *Type 2 Diabetes Mellitus: An Evidence-Based Approach to Practical Management*, the authors of each chapter have synthesized the currently available evidence regarding specific issues in diabetes care. We begin with background information on the epidemiology and pathology of the disease. Following are chapters addressing specific issues in the diagnosis and treatment of type 2 diabetes. Chapters integrating the best evidence for the evaluation and treatment of comorbidities of diabetes, including hypertension, hyperlipidemia, and vascular disease collect a wealth of information in a single resource. Finally, we have highlighted related conditions, including fatty liver disease, pregnancy, and polycystic ovarian syndrome, and barriers to treatment, including stress, depression, and patient motivation. To quantify the strength of evidence supporting current practices, each chapter concludes with a series of recommendations, quantified by their level of evidence as defined in the *Users' Guides to the Medical Literature*, published by the American Medical Association.

The chapters in this book have been written by an interdisciplinary team of scientists and medical professionals. Such an approach emphasizes the need for collaboration in the care of any individual with diabetes and in the effort to find new therapies for the disease. We hope that this reference can provide practical guidance in a single resource for clinicians and scientist alike in our combined endeavor to provide the best care and new opportunities for the treatment of type 2 diabetes.

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Color Plate 2 Glucose and FFA homeostasis (Fig. 1, Chapter 4; *see* complete caption and discussion on p. 50).

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# 1 Epidemiology of Type 2 Diabetes

*Jonathan E. Shaw and Richard Sicree*

***CONTENTS***



**Summary**

This chapter reviews a number of aspects of the epidemiology of type 2 diabetes, and the evidence relating to the major issues. There is strong evidence for a rising epidemic of diabetes in many countries of the world, although the prevalence and incidence of diabetes varies markedly among regions, countries within regions, and by ethnicity. Some of the increase in prevalence is attributed to increased survival with the condition, but it is likely that there is a genuine increase in incidence, associated with lifestyle changes, such as reduced exercise and particularly increased obesity. This also seems to be causing the appearance of type 2 diabetes in new groups, such as children and adolescents, although the older population remains the most affected.

The material linking obesity with type 2 diabetes is overwhelming, as prevalence and incidence studies have both shown strong associations among many ethnicities, and intervention studies have shown benefits of life style modification, through exercise and diet. Specific dietary factors: lower dietary fibre, higher total and lower polyunsaturated fat have all been linked to higher diabetes incidence. These lifestyle factors are closely linked with economic situation in the community, and there is a contrasting pattern between developed and developing countries, such that diabetes is more common amongst the least affluent in developed countries, but increased affluence currently seems to be associated with diabetes in developing countries.

**Key Words:** Diabetes epidemiology; obesity; ethnicity; adolescent; life style; complications.

## INTRODUCTION

Over the last 50 yr, changes in lifestyle have led to a dramatic increase in the prevalence of type 2 diabetes in virtually every society around the world. Reductions in physical activity, increases in dietary intake, and the aging of the population are key factors in bringing about this rapid change. The westernization of diet and of other aspects of lifestyle in developing countries has uncovered major genetic differences in the susceptibility of different ethnic groups to type 2 diabetes. This is most readily apparent in Pacific islanders and indigenous populations in North America and Australasia, among whom type 2 diabetes has gone from being almost unheard of 100 yr ago, to affecting up to 30% of the adult population today. As the prevalence of type 2 diabetes has increased, the age of disease onset has also decreased. The traditional paradigm of type 1 diabetes affecting children or young adults and type 2 diabetes affecting the middle-aged and elderly is starting to change. The increasing numbers of young adults, and even children, who are presenting with type 2 diabetes is blurring the distinction between the 2 types of diabetes and heralds a much longer time for people with type 2 diabetes to develop debilitating complications.

This chapter will describe the epidemiology of type 2 diabetes, including the differing patterns of disease prevalence in different populations, and the main modifiable risk factors that have been identified for type 2 diabetes.

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## GLOBAL AND NATIONAL PREVALENCE OF TYPE 2 DIABETES

The prevalence of diabetes has now been described in many different countries and settings, enabling a good understanding of global disease patterns. Interestingly, most of these large population-based studies do not differentiate between type 1 and type 2 diabetes and simply report the prevalence of all cases of diabetes. However, on the assumption that type 2 diabetes accounts for approximately 90% of all cases of diabetes, these data can be accepted as providing reliable information on type 2 diabetes.

The large numbers of published prevalence reports has allowed several estimates to be made of the global and country-specific burden of diabetes. Recent publications from the World Health Organization *(1)* and from the International Diabetes Federation *(2)* have provided data on the current numbers of people with diabetes, and projections for the year 2025 (Fig. 1 and Color Plate 1, following p. 34). Table 1 indicates that although the methods of the 2 estimates are somewhat different, a high degree of concordance between the 2 sets of findings exists.

The data indicate that a major increase in the numbers of people with diabetes is expected in the next 2 decades. A limitation of the methods used by WHO and IDF needs to be appreciated to understand the findings. Both analyses applied the age-specific prevalences of diabetes (i.e., the prevalence of diabetes within each of a number of age groups) reported in recently published studies to the age structure of the population of each country for the years in question. The predicted change in numbers of people with diabetes over the next 20 yr in this model depends only on the change in age profiles (as well as on changes in urbanization), and assumes that the risk of having diabetes for a 50 year old is the same at the time that the original study was undertaken as it will be in 20 yr time. On the basis of the changes witnessed over the last 20 yr, this appears to be unlikely, suggesting that the projections are likely to be underestimates.

The International Diabetes Federation Atlas for 2006 *(3)* reported national prevalences for adults aged 20–79 yr as varying between 1.5% for the central African state of Rwanda (based on data from Tanzania *(4,5)*) and 30% for the Pacific island of Nauru*(6)*. Low prevalence countries (<2%) in which studies have been performed were, Mongolia *(7)*, Indonesia *(8)*, and Iceland *(9)*, whereas the Middle-Eastern states of the United Arab Emirates *(10)* Bahrain *(11)* and Saudi Arabia *(12–14)*, the Pacific archipelago of Tonga *(15)*, and Singapore *(16)* in South East Asia had prevalences of over 12%, among their adult populations. The IDF analysis also included comparisons of prevalences, based on standardising all rates to a common age and sex structure. This made the emerging

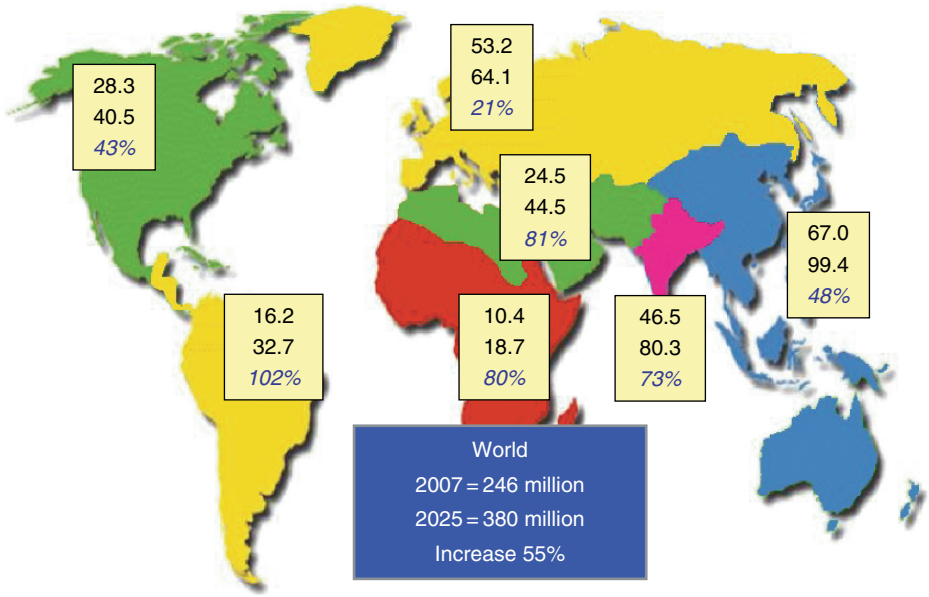


**Fig. 1.** Global projections for the diabetes epidemic: 2007–2025 *(3)* (*see* Color Plate 1, following p. 34).
Data show numbers of people with diabetes (millions) for 2007 and for 2025, as well as the percentage increase between the two time points. Numbers are provided for each of the International Diabetes Federation regions .

**Table 1**
**Global numbers of people with diabetes**

| | *Persons (millions)* | |
|---|---|---|
| | *2000–2007* | *2025–2030* |
| IDF estimates for 2007 and 2025 *(3)* | 246 | 380 |
| WHO estimates for 2000 and 2030 *(1)* | 171 | 366 |

problems in the Middle-Eastern countries even more apparent, and 6 of the 10 countries with the highest diabetes prevalence were in this region. With standardised diabetes prevalences of 20% reported in the United Arab Emirates *(10)*, and 11% in Egypt *(17,18)*, the high rates of diabetes are being seen across the economic spectrum within this region.

## *Regional Prevalences of Diabetes*

### Europe

As in many regions of the world, the prevalence of diabetes varies considerably in Europe. The northern European countries are within the low to moderate range of diabetes prevalence. However, studies from both southern and eastern Europe have higher prevalences, with data from Spain indicating a prevalence of 10.3% in those aged 30–89 yr *(19)*, and from Poland reporting a prevalence of over 15% *(20)*. Ethnic groups originating outside Europe often differ significantly from Europids (people of white European origin) in their risk of diabetes. In the city of Coventry in England, the prevalence of type 2 diabetes was 3.2% and 4.7% respectively in Europid men and women, compared to 12.4% and 11.2% in Asian (predominantly from the Indian sub-continent) men and women *(21)*. The higher prevalence of diabetes in the Asian than the Europid population was not owing to increased obesity, demonstrating, as in a number of other studies, that a lesser degree of excess adiposity is required in Asians than in Europids to precipitate diabetes.

### Africa

Prevalence estimates for diabetes reported for a number of North African countries are in keeping with the high prevalences seen in the ethnically similar countries in other parts of the Middle East. For example, among a population-based sample in Algeria, aged 30–64 yr old, the prevalence of diabetes was 8.2% *(22)*. In Egypt, the prevalence among adults aged 20 yr and older was 9.3% *(17)*, and in Morocco, the prevalence was 6.6% among those aged 20 yr and older *(23)*, and was twice as high in the urban population as in the rural population (9.0 vs 4.4%). This Moroccan study only used a fasting glucose to define diabetes, and so will have underestimated the prevalence that would have been found using an oral glucose tolerance test (OGTT), but nevertheless indicates the magnitude of the burden of diabetes faced by such populations.

Data from other parts of Africa show somewhat lower prevalences of diabetes, with figures of 6.4% for adults aged 25 yr and above in Ghana *(24)*, and less than 1% in Cameroon *(25)*, though more recent data from Cameroon have suggested rates standardised to the world population of 4% *(26)*. Three studies of black South Africans reported prevalences of 4.5% to 8.0% *(27–29)*, and data from the East African country of Tanzania indicate a diabetes prevalence of approx 3.5%*(4)*.

One of the key factors in the measured prevalences of diabetes in Africa, as well as in other parts of the developing world, is the degree of urbanization. Those people living in rural settings, in which high levels of physical activity are part of daily life, have a much lower risk of diabetes than do their urban counterparts. As urbanization and its consequent changes in lifestyle increases in the coming years, the likelihood is that there will be a significant rise in diabetes prevalence.

### Asia

The vast continent of Asia includes many different ethnic groups, as well as many different lifestyles, ranging from the traditional, rural lifestyles to westernized lifestyles in the some of the largest and most densely populated

cities in the world. The high prevalence of diabetes in Middle-Eastern countries has already been described, and in some of these countries, it appears that the clash of a strong genetic propensity to diabetes with urbanization, wealth, and a sedentary lifestyle has produced an epidemic of diabetes, in which, for example, 1 in 5 adults in the United Arab Emirates has diabetes *(10)*. In India, there is little doubt that there has been a rapidly rising prevalence of diabetes in the last 15 yr. Recent data from 6 of the largest Indian cities showed that 12.1% of adults aged 20 yr and older had diabetes *(30)*, and there has been a continuing increase shown for Chennai from 1995 to 2004 *(31)*. In addition to age and obesity being major risk factors for diabetes, higher income was also an important risk factor. Another Indian study showed that in some of the smaller cities (predominantly less than 1,000,000 inhabitants), the prevalence of diabetes among those aged 25 yr and older was lower at 5.9%, and was only 2.7% in rural populations *(32)*. The very pronounced urban-rural and wealth gradient in the risk of diabetes in India once again demonstrates the importance of environmental factors. Because most of the Indian population is currently classified as rural, the potential for a further rise in the national prevalence of diabetes with increasing urbanization is clearly substantial.

In China, the prevalence of diabetes is lower than in India and the Middle East, but at 5.5% *(33)*, is double that reported 10 yr ago *(34)*. Higher prevalences reported in Chinese populations in Singapore, Hong Kong and Mauritius suggest that, as urbanization and westernization proceed, the prevalence in China will rise further. Although urbanization was once again an important risk factor in this study *(33)*, underdiagnosis of diabetes was also identified as a problem. Many population-based studies have found that among all cases of diabetes, approximately half are previously undiagnosed, but in the Chinese study, this figure was 76%.

Perhaps the most concerning diabetes estimate to emerge from Asia is from Cambodia. King et al reported an unexpectedly high prevalence of 5% in a rural setting and 11% in an urban population *(35)*, given the relative poverty and lack of westernization in this country.

### Australasia/Pacific

Although Australia includes a wide range of ethnic groups, including Aboriginals and migrants from Europe, Asia and many other parts of the world, the large majority are from an Anglo-Celtic or other European background, and hence would be expected to have a similar prevalence of diabetes to that seen in Europe. The AusDiab study *(36)* is one of the few nationally representative studies in the world, and reported a prevalence of 7.4% among adults aged 25 yr and over in 1999-2000. Comparison with another Australian study from 1981 *(37)* not only shows that the prevalence of diabetes has risen, but that this is not simply a consequence of the aging of the population. The age-specific prevalence has also risen (Fig. 2): above the age of 35, the prevalence of diabetes is higher within each age group in 1999/2000 than it was in 1981. Figure 2 also demonstrates the strong relationship between age and diabetes, with a rapidly rising prevalence of diabetes seen with increasing age.

The Aboriginal population in Australia, though small, demonstrates up to 30% *(38)* prevalence of diabetes, one of the highest reported anywhere in the world. However, return to traditional lifestyles has been shown to rapidly reverse metabolic abnormalities, with fasting glucose falling from 210 to 120 mg/dL, and fasting insulin falling by 50%, when a group of Aborigines with diabetes returned to a hunter-gatherer lifestyle for 7 wk *(39)*.

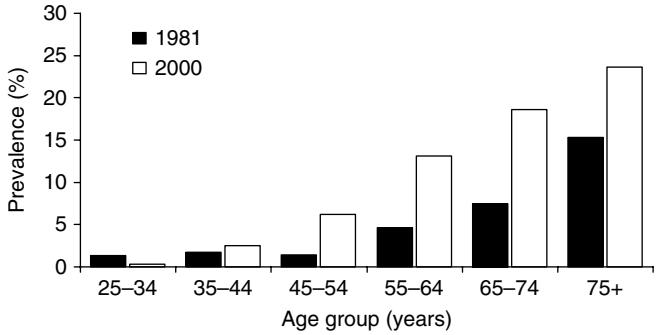


**Fig. 2.** Change in prevalence of diabetes 1981–2000 in Australia *(36)*.

Some of the earliest signs of the modern diabetes epidemic were found in the Pacific islands. The tiny island of Nauru became one of the richest countries in the world (on a per capita basis), as its phosphate deposits were mined. The island underwent major environmental changes after destruction of the reef to allow ships to approach the island, resulting in loss of fishing enterprises, and destruction of agricultural land for mining. Consequently, life became sedentary, and food sources shifted to packaged and canned food supplied from overseas. The traditionally active, healthy, and lean population became markedly obese and was found to have a prevalence of diabetes of 11% in those aged 25–34 yr old, rising to 56% in those aged 55–64 yr old *(40)*. Other island populations in the Pacific have also experienced major social and environmental changes, with concurrent increases in the prevalence of diabetes.

### North America

Data from the National Health and Nutrition Examination Survey (NHANES) series of surveys have provided a clear picture of the epidemiology of diabetes within the US. The rise in diabetes prevalence over the last 30 yr has occurred in parallel with a rise in the prevalence of obesity. The most recent estimates put the prevalence of diabetes at 9.3% for adults aged 20 yr and older *(41)*. Of the largest population groups in the US, the highest prevalence is seen in African Americans (11.0%) followed by those of Mexican origin (10.4%), with Europids (non-Hispanic whites) being at the lowest risk (5.2%) *(41)*. Figure 3 shows the prevalence of diabetes according to ethnicity within the US and demonstrates that as the proportion of people of Hispanic ethnicity increases, so the national prevalence of diabetes will rise.

However, Native American populations have by far the highest diabetes risk in the US, with the highest diabetes prevalence in the world being recorded in the Pima Indian population of Arizona. More than 20 yr ago, the prevalence in this population was found to be 50% in middle-aged adults, with an incidence that was 19 times greater than the predominantly white population of Rochester, Minnesota *(42)*. Similar, though not quite so spectacularly high diabetes prevalences have been recorded in other Native American groups, in the United States, as well as in Canada.

The diabetes prevalence in the US is one of the highest in the developed world, reflecting not only the high prevalence of obesity, but also the significant proportion of the population belonging to high-risk ethnic groups. If migration and differential birth rates lead to a further increase in the size of these groups, particularly in the Hispanic population, further rises in diabetes prevalence can be expected.

Recent data from very large, national studies in Mexico revealed a prevalence of 8.2% *(43)* and a similar prevalence of about 9.0% *(44)*. Although these figures are marginally lower than that reported for the US, the Mexican population age structure is much younger than that in the US; hence, the age-specific prevalences are higher in Mexico. For example, among those aged 40–59 yr, the prevalence of diabetes was 7.9% for non-Hispanic whites in the US *(41)*, but approx 15.3% for Mexican Americans, which was similar to the prevalence for this age group in the 2 Mexican studies *(43,44)*.

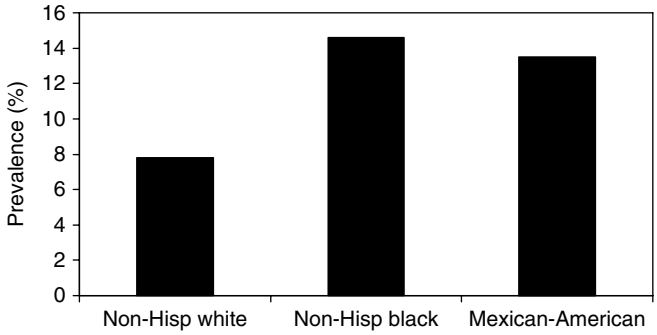


**Fig. 3.** Prevalence of diabetes according to ethnicity in the USA *(41)*.

### South and Central America, and Caribbean

Data from this region are relatively limited, but a study from Jamaica found diabetes in 13.4% of adults *(45)*, with those in the top quartile of BMI having a 3.3–5.4-fold higher risk of having diabetes than those in the lowest quartile. In Brazil, a study from 9 large cities found that the prevalence of diabetes was 7.6% with no differences observed between the prevalence in whites and in nonwhites *(46)*. Very similar findings were reported from Argentina, where the prevalence in a population drawn from 4 cities was 6.5–7.7% *(47)*, and from Colombia, with a prevalence of 7% *(48)*.

## *Changes in the Prevalence of Diabetes Over Time*

Estimates of the global burden of diabetes have frequently concluded that the prevalence of diabetes is rising, but these conclusions are not always based on studies that can be directly compared. However, a number of pairs or series of studies do allow a more accurate assessment of changes over time. Between 1976 and 1988, the prevalence of diabetes among people age 40–74 yr rose from 11.4% to 14.3% in the US *(49)*. More recently the 1988–1994 (NHANES III) and NHANES 1999–2000 were compared, indicating a statistically nonsignificant increase from 8.2% to 9.3% for diabetes in the 20 year and older population *(41)*, suggesting that the rate of rise of diabetes prevalence may be slowing. The changing prevalence over time in the US illustrates not only the effects of increasing obesity and aging over time, but also the impact of a changing ethnic mix. In Australia, an estimated 7.4% of adults in the year 2000 had diabetes, compared to an estimated 3.4% in 1981 *(36)*. A report from Denmark directly compared the prevalence of diabetes and impaired glucose tolerance (IGT) *(50)* between 2 cohorts of 60 year olds: the former in 1974/5, and the latter in 1996/1997. Overall, the rates of abnormal glucose tolerance (either diabetes or IGT) had increased by 55% ($p < 0.001$). Data from 2 population-based surveys in the south Indian city of Chennai revealed a diabetes prevalence rising from 8.2% in 1988/1989 to 11.6% in 1994/1995 *(51)*, with a further survey in the same city carried out in 2003/2004 reporting a diabetes prevalence of 14.3% *(31)*. A series of 3 surveys conducted in the Indian Ocean island of Mauritius has shown the prevalence of diabetes to have risen from 12.8% in 1987 to 15.2% in 1992, and 17.9% in 1998 *(52)*.

In China, national surveys assessing the prevalence of diabetes were conducted in 1994/1995 and 2000/2001 *(33,34)*. The 1994/5 survey involved more than 200,000 participants, and based the prevalence on the 2-h plasma glucose value following the oral glucose tolerance test, or on previously diagnosed diabetes. The national prevalence for the 25–64 year old population was 2.5%. The 2001 survey used the fasting criterion recommended by the American Diabetes Association (ADA) *(53)* (fasting plasma glucose $\geq$ 7.0 mmol/L), and was conducted on an older subgroup (35 – 74 yr), but even among those in the 35–64 range, the overall prevalence was about 50% higher than detected previously. In both surveys only about one third of persons with diabetes had been previously diagnosed; the others having diabetes detected at the examination. There was little gender difference, but urban prevalence was higher than rural, when analyzed for the 2001 survey.

Although there is little doubt that there is a major genetic component to the etiology and development of type 2 diabetes, the rapid rise in the prevalence of type 2 diabetes witnessed in recent decades indicates the importance of environmental influences. The time period is far too short to have seen any significant shift in the gene pool, but huge changes in lifestyle, with increasing mechanization of manual tasks and of transport, and a rise in caloric intake has led to increasing obesity, and an epidemic of diabetes. The intertwining of the effects of genes and the environment is illustrated by the higher prevalences of diabetes in people of Indian compared to Europid (white European) origin that is so frequently observed, within urban settings. For example, Indians from the city of Chennai have a diabetes prevalence of 11–14% *(31,51)*, whereas many European countries have a prevalence of under 8% *(1,3)*. Several direct comparisons, within the same country or region have also shown that Hispanics and ethnic groups originating from India have a higher diabetes prevalence than do Europids *(21,49)*.

### Rising Prevalence: Owing to Increasing Incidence or Better Survival?

The above data show an increase in diabetes prevalence (i.e., the percentage of a population that has diabetes at a given point in time), occurring in almost all countries, which is usually assumed to be primarily owing to increasing incidence (i.e., an increase in the number of new cases of diabetes developing each year), but could also be a consequence of reduced mortality. Thus, it is possible that with no change in the rate of new cases

developing, the total number of individuals with diabetes within a population could rise if diabetes mortality were to fall (as a result of improved treatment). The burden of diabetes within a population depends on the prevalence and is undoubtedly climbing, but understanding the reason for the rising prevalence is important for understanding how to reverse the rise in prevalence.

Rising incidence generally results from a worsening of the risk factor profile of a population (in the case of diabetes, this would include increasing obesity, age and sedentary habits), whereas reduced mortality reflects either the disease becoming less harmful, or an improvement in the care provided for those with the disease. There have been a number of opinions as to the main reasons for the increasing prevalence of diabetes *(54–57)*, particularly as to whether it is based on an increase in incidence. Green et al analyzed Danish data examining the numbers of people commencing pharmacological treatment for diabetes, and the mortality of those individuals *(55)*. The undoubted rise of approx 50% over 10 yr in the numbers of people with drug treated diabetes was explained by an almost constant incidence of drug treated diabetes over the 10 yr, which exceeded a slowly falling mortality rate.

Based on modeling with different age and prevalence patterns for westernized and developing region populations, Colagiuri et al *(54)* concluded that demographic changes were insufficient to explain the documented rises in prevalence, and that there was good evidence of rising incidence. Unfortunately, although there are many cross-sectional studies of prevalence, there are very few true incidence studies, and so analyses on this important issue often use surrogates such as the incidence of drug-treated diabetes, which clearly can vary for many reasons other than a change in the actual incidence of diabetes. Wareham and Forouhi *(57)* highlighted this need for better data to establish which are the principal factors underpinning the rising prevalence. What is clearly needed is age-specific incidence data for the same populations, separated in time, but likely to have experienced life style and/or other risk factor changes. Ideally, this should be part of a formal surveillance program, rather than ad hoc research studies.

### *Type 2 Diabetes in Children and Adolescents*

One of the most alarming consequences of the diabetes epidemic is the appearance of type 2 diabetes in children and adolescents *(58,59)*. Until a decade or so ago, type 2 diabetes was regarded as a disease of the middle aged and elderly. Although it still is true that this age group maintains a higher relative risk (in relation to younger adults), there is accumulating and disturbing evidence that onset in the 20 to 30 yr of age group is increasingly seen *(59,60)*. Now, even children are becoming caught up in the type 2 diabetes epidemic. Although type 1 diabetes remains the main form of the disease in children worldwide, it is more than likely that within 10 yr type 2 diabetes will be the more prevalent form in many ethnic groups, potentially including Europid groups *(61)*. There are now numerous reports of type 2 diabetes in children from countries including Japan, the United States, Pacific Islands, Hong Kong, Australia, the United Kingdom and Taiwan *(59,60,62–64)*. Dabelea and coworkers have reported on changes in rates of diabetes in Pima Indian children over a 30 year period *(65)*. They have demonstrated rising rates of glucose intolerance with time and age, as well as a female preponderance. From 1967-76 to 1987-96 the prevalence of type 2 diabetes in children markedly increased from 2.4% in males and 2.7% in females to 3.8% in males and 5.3% for females.

Precise estimates of the prevalence of type 2 diabetes in children and adolescents remain few and far between, but nevertheless some indication of the magnitude of this growing problem is available. Data from a survey of 3 million children in Taiwan *(66)* found the annual rate of newly identified diabetes to be 9.0/100,000 boys and 15.3/100,000 girls. In the US, national data from 1988–1994 *(67)*, and data from a single school district *(68)* collected approx 10 yr later showed diabetes prevalences of 0.13% and 0.4% respectively. Clinic studies from the US *(69)*, Thailand *(70)* and New Zealand *(71)* have shown that, of all new referrals to clinical diabetes services, the proportion that are for type 2 diabetes has risen markedly over recent years such that, by the end of each observation period, type 2 diabetes accounted for 18-35% of the new cases presenting to these clinics. However, not all populations are witnessing such a marked rise in type 2 diabetes among children and adults. Well-designed studies from Germany, Austria, France and the UK *(72–74)*, reporting data from diabetes registers and from multiple diabetic clinics show type 2 diabetes accounting for only 1–2% of all cases of diabetes. Nevertheless, even in these lower-risk European populations, where most of the cases of type 2 diabetes have occurred in

children from high-risk ethnic groups, a small number of cases of type 2 diabetes have occurred in Europid children.

The emergence of type 2 diabetes in children brings a serious new aspect to the diabetes epidemic and heralds an emerging public health problem of major proportions in the pediatric area. The rise of type 2 diabetes in this age group is mainly owing to the increase in time spent on sedentary activities such as television and computer usage, either for games or school-work, with consequent reduction in sports. The additional effects of diets high in energy, carbohydrate, and fat simply add to the risk of developing diabetes and obesity.

This fall in the age of onset of type 2 diabetes is an important factor influencing the future burden of the disease. Onset in childhood heralds many years of disease and an accumulation of the full range of both micro- and macrovascular complications *(61)*. The American Diabetes Association (ADA) and the American Academy of Pediatrics have published a consensus statement on the problem *(62)*. A key area raised in this report is the issue of poor compliance with diet and pharmacological therapies. Recently, a number of pharmaceutical companies have embarked on clinical trials of oral hypoglycaemic agents to check their safety and efficacy in this age group as they may face up to 40–50 yr of therapy.

Another worrying aspect is the high risk of, and early appearance of long term micro- and macrovascular complications in the adolescent and early adult years. As with adults, it is expected that youth with type 2 diabetes will also develop diabetes related micro- and macrovascular complications. This was reported recently in a study from Canada, where subjects who developed type 2 diabetes as children were then surveyed as young adults, aged between 18 and 33 yr. Of the 51 subjects reviewed, 9% had died, 6% were on dialysis, while one had a toe amputation and one was blind *(75)*.

Another follow-up study from Japan compared those with type 1 and type 2 diabetes diagnosed under 30 yr of age for the development of nephropathy *(76)*. After 30 yr of diabetes, 44% of those with type 2 and 20.2% of those with type 1 had nephropathy. Yet another study *(77)* looked at the incidence of retinopathy and nephropathy among Pima Indians diagnosed with type 2 diabetes under 20 yr of age (youth), 20–39 yr (young adults) and 40–59 yr of age (older). At less than 5 yr duration of type 2 diabetes, nephropathy had developed at a similar rate in all age groups (incidence/1,000 person years: 13/1,000 youth, 8/1,000 young adults and 7/1,000 older). However, retinopathy was not apparent in those with youth onset diabetes for less than 5 yr, and only appeared among this group after 5–10 yr duration (incidence/1,000 person years: 10/1,000 youth, 29/1000 young adults and 35/1,000 older). A study of New Zealand Maori diagnosed with diabetes before the age of 30 compared the prevalence of several diabetic complications between those with type 1 and those with type 2 diabetes *(78)*. Not only was type 2 more common among this population, but the prevalences of nephropathy and retinopathy were higher in those with type 2 diabetes, and the prevalence of hypertension also greater. Data from Taiwan indicate that compared to children with normal glucose tolerance, those with type 2 diabetes have a 70% increased risk of having hypertension and an 80% increased risk of having an elevated serum cholesterol *(66)*.

These studies have important implications in that they highlight the risk of complications occurring at a relatively young age and, as in the case of the Pima Indian study, that these complications can occur relatively soon after diagnosis. The data on complications confirm that type 2 diabetes in children and adolescents is not a mild and benign elevation of blood glucose. Rather, it carries at least as high a risk of microvascular complications as is seen in type 1 diabetes, and predisposes to premature vascular disease in the form of hypertension and dyslipidemia. In this population, complications of diabetes occur as these people enter their peak working and earning capacity, potentially increasing the burdens on health budgets and society as a whole. Early detection and intervention is therefore essential to reduce the risk of future complications.

### *Type 2 Diabetes in the Elderly*

As seen in Fig. 2, the risk of developing diabetes rises sharply with increasing age, rising in Australia from 0.3% in the 25-34 year old age group to 23.6% in those over 75. Among the over 75s, when the prevalence of impaired glucose tolerance and impaired fasting glucose is added to the figure for diabetes, the prevalence of abnormal glucose metabolism is 53% *(36)*. In this age group, it is clearly normal to be abnormal. It should be noted that, in some populations, there is a reduction in the prevalence of diabetes in the oldest age group, compared to the prevalence in the middle-aged. This is likely to be owing to a survivor effect, in which those with

diabetes are less likely to survive into old age, and so the prevalence of diabetes among those who do survive into old age is slightly lower than in younger age groups.

The elderly would also be expected to suffer significantly from the morbidity associated with diabetic complications, as their age and other comorbidities provide additional risk. However, the effect of 'competing morbidities' may also mean that the impact of any single disease in the elderly is less than in younger people. Furthermore, in considering the impact of diabetes on morbidity and mortality in the elderly, it may be important to differentiate between those elderly people who have had diabetes for many years and those who only develop diabetes when they are older.

A recent meta-analysis of studies on mortality among people developing diabetes over the age of 60 has, in fact, confirmed that the impact of diabetes on total mortality seems to fall with increasing age of onset of diabetes *(79)*. In comparison to nondiabetic populations, the relative risk (with 95% CI) of mortality for men diagnosed between the ages of 60 and 70 was 1.38 (1.08–1.76) and for men diagnosed aged 70 yr or older was 1.13 (0.88–1.45). The findings for women were similar, with relative risks of 1.40 (1.10–1.79) and 1.19 (0.93–1.52) for the 2 age groups respectively.

## *Etiological Factors in the Development of Type 2 Diabetes*

### Environmental Factors

**Obesity.** There is an enormous amount of evidence implicating obesity in the development of diabetes. This includes population studies comparing rates of obesity and of diabetes across different populations, cross-sectional and longitudinal studies within populations, and intervention studies assessing the impact of weight loss. Those populations with the highest rates of diabetes, such as the Pima and Nauruans, also have very high rates of obesity. Similarly, populations with low rates of obesity tend to have low prevalence of diabetes.

More significantly, studies within populations tend to show a gradation of diabetes prevalence, with diabetes being markedly less common at all ages among the leanest members of the population. This association has been demonstrated in most ethnicities and populations. Longitudinal studies also show increasing likelihood of development of diabetes according to obesity level. Data from the Nurses Health Study *(80)* demonstrate that, with increasing body mass index (BMI), the risk of developing diabetes increases. It is interesting to note that in this large, prospective study, the excess risk is not restricted to those in the obese category (Fig. 4). Indeed the risk of developing diabetes appears to be related to BMI in a continuous fashion, such that even a BMI of 24 kg/m$^2$, which is usually considered to be within the "normal" range, carries a greater risk of developing diabetes than does a lower BMI.

The duration of obesity is also important. Data from a study from Israel *(81)* show that, for any current BMI, a greater BMI 10 yr previously increased the risk of developing diabetes. Randomized controlled clinical trials (RCT) provide further robust evidence of the link between obesity and diabetes. Intensive lifestyle interventions in those with impaired glucose tolerance and obesity have focused on dietary change, increased physical activity and weight loss *(82,83)*. With weight loss targets of 5–7%, and achieved weight loss of approx 5%, both the Finnish *(82)* and the American *(83)* studies showed a 58% reduction over 4–6 yr in the incidence of diabetes among those in the intensive lifestyle study arms compared to those in the control arms. Furthermore, a placebo

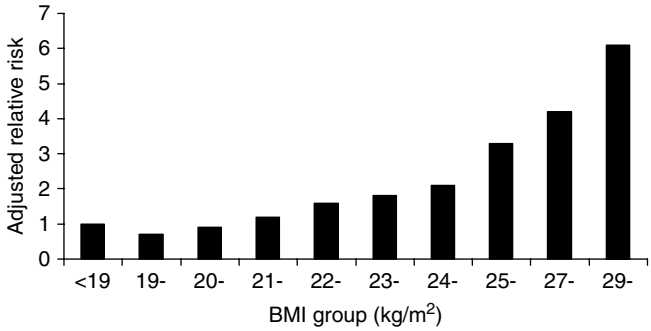


**Fig. 4.** The age-adjusted risk of developing diabetes over 8 years, according to baseline BMI. The nurse Health Study *(80)*.

controlled RCT of the weight loss drug orlistat showed a 37% reduction in the incidence of diabetes and a 45% reduction within the subgroup with IGT *(84)*.

### Type and Measurement of Obesity

In the last 10–15 yr, it has become apparent that different fat depots have different properties. In particular, visceral fat has been found to be more metabolically active than subcutaneous fat. Circulating free fatty acids (FFAs) (as well as inflammatory cytokines) encourage insulin resistance in liver and muscle and are released at a greater rate by intra-abdominal compared to subcutaneous adipocytes. Furthermore, central fat deposits release FFAs into the portal circulation, which drains directly into the liver, further promoting hepatic insulin resistance and hyperglycemia. A study of second generation Japanese Americans showed that visceral fat, as measured by intra-abdominal fat area on CT scanning, predicted the development of diabetes, although other measures of total adiposity, including BMI, did not *(85)*. For those of third generation Japanese descent, all the measured indicators of obesity were predictive of diabetes incidence. A number of large observational studies have relied on anthropometric measurements of adiposity to compare the impact of overall adiposity (as determined by BMI) with that of visceral adiposity (as measured by the waist circumference or the waist:hip ratio (WHR)) on the development of type 2 diabetes. Cross-sectional data from a study in Mauritius *(86)* showed that both BMI and WHR were independently associated with the presence of diabetes, with WHR being more important in women, and BMI more important in men. In the Health Professionals Follow-Up Study of over 27,000 men, waist circumference (WC), WHR, and BMI predicted the development of diabetes over 13 yr, with the risk being 7–12 times higher in those in the top quintile of each measurement, compared to those in the bottom quintile *(87)*. Among those who were obese according to the BMI (BMI $\geq$ 30 kg/m$^2$), the risk of developing diabetes varied considerably according to the WC. However, the opposite was also true, in that for those with a WC $\geqq$102 cm (i.e., within the obese range), the risk also varied according to the BMI. Overall, BMI and WC were better predictors than was WHR, but it appears that each of the measures provides information about the risk of diabetes that is not captured in the other (i.e., they are statistically independent of each other). This is consistent with the hypothesis that both subcutaneous and visceral fat depots play a role in the development of diabetes. However, if one were to accept that, pathophysiologically, visceral fat is the key fat depot, an alternative explanation is that the inherent difficulties in accurately measuring WC mean that it is a relatively poor measure of an important physiological parameter (visceral fat), although BMI is a good measure of a less important physiological parameter (total fat), which itself is correlated with visceral fat.

## *Physical Activity and Exercise*

Contracting skeletal muscle takes up more glucose from the circulation than it does at rest. This effect is partly mediated by adrenaline, and is responsible for the state of improved insulin sensitivity that is produced by exercise. The increased glucose uptake continues after exercise has been stopped, to replenish glycogen stores, and so regular exercise has the potential to improve carbohydrate metabolism in both diabetic and nondiabetic subjects. In addition, it has beneficial effects on lipid metabolism and its contribution to weight loss provides another mechanism whereby exercise may influence the development of type 2 diabetes.

Cross-sectional population based comparisons of diabetic with normoglycemic subjects have shown associations of diabetes with various different assessments of physical activity in populations as diverse as Asian Indians, Alaskan natives, and Chinese subjects. Prospective studies identifying risk factors for the development of type 2 diabetes in normoglycemic subjects also find physical activity to be correlated. In a large study of US male physicians, vigorous activity undertaken at least once a week led to a relative risk of developing type 2 diabetes of 0.71 (after adjusting for age and BMI), in comparison to those exercising less frequently *(88)*. The effect was strongest in the most obese. A very similar result was found among a cohort of over 85,000 women *(89)*, but the effect was significantly weakened after controlling for BMI. Moderate physical activity in British men also reduced the relative risk to 0.4 *(90)*. Direct measurements of physical fitness have also been shown to be predictors of type 2 diabetes, and although less practical for screening programs, seem to provide more information than do physical activity scores.

Further evidence of the important role that exercise plays has recently been presented in RCTs targeting the prevention of diabetes. In studies from the US and Finland, lifestyle interventions that included both dietary

change and increases in exercise levels led to a reduction in the incidence of diabetes of 58% among obese people with IGT *(82,83)*.

Recently, an additional component to the role of physical activity in the development of diabetes and obesity has been identified. Measurements of sedentary behavior have been found to be independent predictors of obesity and of abnormal glucose tolerance. Cross-sectional studies have related the amount of time spent watching television to the risk of obesity and of having IGT or diabetes and have found a significant relationship *(91,92)*. Indeed, the relationships appear to be stronger for television viewing time than they are for time spent undertaking physical activity. This suggests an additional health message focusing on avoiding sedentary behaviors in addition to the promotion of exercise sessions.

**Dietary Factors.** There seems to be little doubt that diet plays a significant role in the development of type 2 diabetes. However, it has been remarkably difficult to pin down the precise dietary constituents that are the key players. There are several reasons for this. Observational studies relate measurements of potential risk factors to outcomes, and rely on accurate measurements of both. Precise measurement of dietary intake has been particularly challenging, and although a variety of validated questionnaires have been developed to assess food intake, their accuracy is always limited by the ability of individuals to recall their intake and is also influenced by the patient's perceived rather than actual diet. Furthermore, observational studies can be confounded by associations with other factors. This is neatly demonstrated by the case of hormone replacement therapy (HRT). A number of large, well-conducted observational studies reported that women who were on HRT had lower rates of CVD and some cancers than women not using HRT, and concluded that HRT was protective against these diseases. However, clinical trials showed the opposite —women randomized to HRT actually had slightly higher rates of CVD and cancer than those on placebo *(93)*. Thus, it is clear that although the reports from observational studies had attempted to adjust, statistically, for the fact that women who chose to go onto HRT might also have made a variety of other healthy lifestyle choices, which in themselves might reduce disease risk, this was never fully achieved, and led to an erroneous conclusion. RCTs provide an opportunity to assess causality, not just correlation. However, they also have some pitfalls. Although different groups within an RCT will be "instructed" to follow different diets, final results ultimately reflect the "achieved" diet (which, as described above, is difficult to measure), rather than the prescribed diet. Additionally, a number of studies of diet within the diabetes field have used diet as one component of a lifestyle program, making it difficult to tease out the precise roles of specific dietary components. With these limitations in mind, it is reasonable to draw some conclusions from the literature.

*Observational Studies.* The increased risk of diabetes with increasing intake of total fat has been reported in several studies using prospective data *(94,95)*. However, this has not been a consistent finding, with other studies failing to find the link *(96,97)*. A higher intake of saturated fat has also been associated with type 2 diabetes *(98)*, whereas higher intakes of unsaturated fats appear to be protective, with those people in the top quintile of polyunsaturated fat intake having a 25% lower risk of developing diabetes compared to those in the bottom quintile *(97)*. There may also be a role for trans fatty acids, which may also increase the risk of developing diabetes, with those in the top quintile of trans fatty acid intake having a 31% higher risk of developing diabetes compared to those in the bottom quintile *(97)*.

The relationship of carbohydrate intake to diabetes is less clear than for fat intake, with a recent review concluding that there was no association between total carbohydrate intake and diabetes risk *(99)*. However, there seems to be a fairly consistent finding in terms of the importance of dietary fiber. Three large longitudinal studies showed that a low intake of dietary fiber increased the risks of developing diabetes *(96,100,101)*, such that those who were in the lowest quintile of dietary fiber intake had a 39–56% increased risk of developing diabetes, compared to those in the highest quintile of fiber intake.

*Randomized controlled trials.* The most robust data on lifestyle factors in the development of diabetes come from the diabetes prevention trials. There are now several such studies, each of which has convincingly shown that lifestyle changes focusing on weight loss, dietary change, and increasing physical activity, significantly reduce the risk of progressing to diabetes among people with IGT *(82,83,102,103)*. The dietary targets of the Finnish DPS *(82)* were similar to those used in other studies, and included total fat intake <30% of energy intake, saturated fat intake <10% of energy intake, and fiber intake >15g/1,000 kcal. These targets, in combination with a weight loss and a physical activity target, led to a 58% reduction in the rate of developing diabetes. Furthermore, the risk of

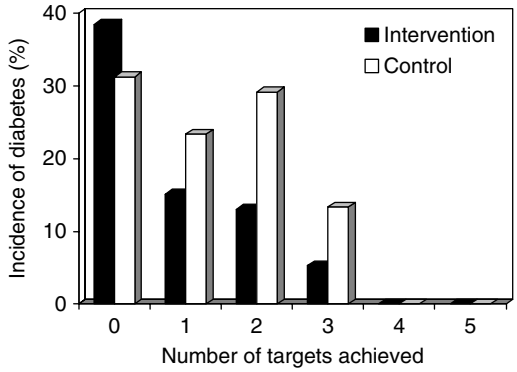


**Fig. 5.** The incidence of diabetes according to the number of lifestyle targets achieved. The Diabetes Prevention Study *(82)*. Data shown for the intervention and control arms of the clinical trial.

developing diabetes fell progressively with increasing numbers of targets achieved (Fig. 5). Thus, it appears that each of the targets was contributing to the prevention of diabetes, and it is therefore reasonable to conclude that increased dietary fat and reduced levels of dietary fiber are important etiological factors in the development of type 2 diabetes.

## Sociocultural Factors

Although much of the focus of research into the etiology of diseases such as diabetes is usually on the biomedical risk factors, and the unraveling of molecular mechanisms, sociocultural factors can also play a major role. The impact of urbanization and westernization has already been referred to above. For many societies the switch from traditional lifestyles to modern, urban lifestyles has altered dietary habits, markedly reduced physical activity, and changed many of the long-established social norms, resulting in an explosion of diseases such as type 2 diabetes and obesity. In the Pacific island of Nauru, diabetes was almost unheard in the early part of the 20th century, but by the 1970s and 1980s was affecting 1 in 4 of the adult population *(40)*. Indians living in large cities have 4 times the prevalence of diabetes seen in their rural counterparts *(30,32)*, whereas in Cambodia, the prevalence of diabetes is twice as high in an urban population as in a rural population *(35)*.

The influence of the environment is not limited to the westernization of lifestyle, but even within apparently similar environments, measures of socio-economic status are related to diabetes. A study from the north of England found that the prevalence of type 2 diabetes was nearly 30% higher in people living in areas with the worst quintile of deprivation scores, compared to those in the most affluent areas *(104)*. Interestingly, there was no association between the prevalence of type 1 diabetes and deprivation. Similar findings were reported in a study based on a diabetes register in Scotland *(105)*. Those in the most deprived areas were approx 60% more likely to have type 2 diabetes than were those in the least deprived areas. Once again, no association with deprivation was observed for type 1 diabetes. In a study based in general practice in Spain, the same relationship was observed for type 2 diabetes, with the strength of the association being stronger in women than in men *(106)*.

In contrast, the impact of poverty and socioeconomic status operates in the opposite direction in the developing world. In a study from the south of India, those in the high income group were twice as likely to have diabetes as were those in the lower income group *(107)*. Similarly, a large study from China showed that the prevalence of diabetes was higher in those with the highest income *(34)*.

How can this apparent paradox be resolved? The most likely explanation is that measures of socioeconomic status are markers for different health-related behaviors in different settings. In the developed world, where automation and mechanization are features of life across the socioeconomic gradient, those in areas of deprivation have poorer access to healthcare and to health information, and may consume less healthy diets because of the low cost of energy-dense, high fat foods. Hence the risk of diabetes is higher in lower socio-economic areas. In the developing world, however, poorer people will often be employed in manual work, and have only limited access to labor-saving devices. Living in rural and more traditional environments is also likely to be associated

with consuming more traditional diets incorporating more fruit and vegetables. Thus, in this setting, it is the wealthy, with ready access to labor-saving devices and westernized food, who run the highest risk of developing type 2 diabetes.

## SUMMARY

Lifestyle changes, together with the aging of populations, has led to a huge increase in the numbers of people with diabetes worldwide. As a westernized, sedentary lifestyle has spread across the globe, the prevalence of type 2 diabetes has risen, particularly among non-European ethnic groups. This disease of the middle-aged has gradually involved younger and younger adults, and is now even appearing in adolescents and children. If there is to be any reversal of this relentless increase in the numbers with diabetes, it seems likely that the necessary lifestyle changes will require interventions at both personal and societal levels.

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# 2 Pathogenesis of Type 2 Diabetes Mellitus

*Jack L. Leahy*

***CONTENTS***



**Summary**

The pathophysiology of type 2 diabetes is complex, with many different elements acting to cause the disease. This review proposes a sequence of events that is based on a careful analysis of the human and animal model literature. It seems certain that a genetic predisposition is needed although, until recently, little was known about specific genetic mutations. Whether the diabetes phenotype then occurs depends on a large number of environmental factors that share an ability to stress the glucose homeostasis system by promoting insulin resistance or worsening ß-cell function. We propose that a lowered ß-cell mass through genetic and/or ß-cell cytotoxic factors is an important predisposing factor for glucose intolerance. As the blood glucose level rises to a minor degree above normal, acquired defects in the glucose homeostasis system occur—a key early one is an impaired first phase insulin response to a meal —that cause the blood glucose level to rise further into the prediabetes range. This increase in glycemia, perhaps in concert with hyperlipidemia, causes additional deterioration in ß-cell function and, to a smaller extent, resistance, resulting in a blood glucose level that continues to rise to full blown diabetes. This sequence provides insight into prevention and treatment of type 2 diabetes. One can modify predisposing environmental factors, although that is not easily done. Alternatively, one expects that, as the molecular basis for the organ dysfunctions are discovered (ß-cell dysfunction and death, and muscle and hepatic insulin resistance), novel therapies will be developed that target those defects.

**Key Words:** ß-Cell dysfunction; insulin resistance; glucose toxicity; lipotoxicity; ß-cell apoptosis.

## INTRODUCTION

Type 2 diabetes is a worldwide health crisis. In the U.S., 20.8 million are affected at a cost of $132 billion in 2002 *(1)*, and the numbers will likely continue to increase. The Centers for Disease Control and Prevention estimates there are more than 40 million people in the U.S. with prediabetes. Given that the Diabetes Prevention Program showed an 11% yearly conversion rate of impaired glucose tolerance (IGT) to diabetes *(2)*, there could be as many as 4 million new cases each year. Furthermore, the incidence of type 2 diabetes is rising around the world *(3)*, with a recent prediction that the worldwide prevalence will increase from 2.8% in 2000 to 4.4% in 2030, resulting in 366 million affected people *(4)*.

Much of the current crisis stems from our modern lifestyle. Furthermore, the global shift from an agrarian existence to city living, resulting in less physically demanding office and factory jobs, is taking its toll. In the U.S.,

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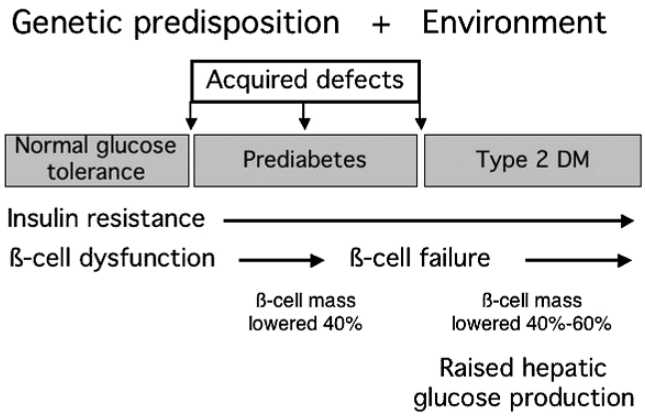


**Fig. 1.** Proposed sequence of the key pathological features of type 2 diabetes as discussed in this review.

these changes have been most evident in children—numerous studies have reported the epidemic of childhood obesity *(5)* and its root causes of reduced physical activity and high caloric intake *(6,7)*.

Although returning to healthy lifestyles likely would reverse the rising incidence of type 2 diabetes, this may be an impractical solution. Instead the current focus is to investigate the pathogenesis, hoping to develop pharmaceuticals that target the key pathogenic elements. We entered the 1990s knowing that type 2 diabetes was characterized by the triad of ß-cell dysfunction, excess glucose production from the liver, and insulin resistance, defined as impaired insulin-mediated glucose clearance into skeletal muscle *(8)*. However, the link among these organs was unknown. Considerable insight has been gained over the last decade, although much remains to be learned. This review provides an overview of the current understanding of the pathogenesis of type 2 diabetes (Fig. 1). A major focus of the proposed sequence relates to defects in the mass and function of islet ß-cells, as they are known to be important elements in the early stages of the disease.

## GENETIC PREDISPOSITION

The fact that type 2 diabetes is a genetic disease was confirmed more than 2 decades ago by a famous study of identical twins in the U.K. that found essentially a 100% concordance rate *(9)*. However, this kind of study provides no insight into the underlying genetic defect (s) either directly impairing the glucose homeostasis system or causing insulin resistance or another defect that exceeds the capacity of a normal glucose homeostasis system. With the advent of molecular biology, the basis is now known for many monogenic forms of diabetes, such as mitochondrial genome defects and their association with diabetes and deafness *(10)*, Wolfram's syndrome *(11)*, several syndromes of extreme insulin resistance *(12)*, and most of the MODY syndromes *(13)*. Still, these account for only a small proportion of diabetes cases.

In contrast, genetic insight into type 2 diabetes has been frustratingly slow. One identified gene is *calpain 10*, a member of a ubiquitously expressed family of cysteine proteases. In the mid 1990s, linkage analysis identified a locus on chromosome 2 that was calculated to account for about 30% of type 2 diabetes in Mexican-Americans *(14)*. The specific gene was later shown to be calpain 10 *(15)*. However, the role of calpain 10 in glucose homeostasis remains unclear, with a current focus on a regulatory role in insulin exocytosis *(16)*.

A recent study of isolated islets from humans with type 2 diabetes reported a 90% reduced mRNA expression of aryl hydrocarbon receptor nuclear translocator (*ARNT),* a transcription factor previously unknown to the diabetes field *(17)*. Mice were created with a ß-cell specific knockout of the *ARNT* gene. These animals developed glucose intolerance and impaired glucose-induced insulin secretion, along with a ß-cell mRNA expression profile that closely matches the human type 2 diabetes islets. Considerable interest was generated by these findings, and a role for *ARNT* in type 2 diabetes is under investigation.

Other chromosomal "hot spots" have been identified in various populations, and looking for the specific genes is now much faster because of the human genome project. Also, many research groups have focused on various gene polymorphisms. To date, all have lacked a strong association with type 2 diabetes after rigorous study. An

example is *Insulin Receptor Substrate-1* (IRS-1), the first downstream intermediate from the insulin receptor in the insulin action cascade. A common IRS-1 polymorphism was proposed to influence the kinetics of insulin secretion *(18)*, but a large study failed to show a link with type 2 diabetes *(19)*. Current polymorphisms of interest are the transcription factors *TCF7L2 (20)* and *KLF11 (21)*, and the *Kir6*.2 subunit of the ß-cell $K^+_{ATP}$ channel *(22,23)*.

Finally the breakthrough occurred in 2007 with the advent of genome-wide association screens for common diseases including type 2 diabetes. Unlike prior genetic studies that often tested for genes that seemed plausible as causing a predisposition for type 2 diabetes (so-called *candidate gene approach*, but in reality guesses), this kind of study uses small nucleotide sequences that are spaced throughout the whole genome to search for patterns that track with a disease such as type 2 diabetes, and thus identify regions in which to look for a predisposition gene. And they have been amazingly successful. In less than a year, 6 genome-wide association studies that examined 7,200 cases of type 2 diabetes and 12,000 controls in several population groups have identified 11 predisposition genes (reviewed in *163*). Plus the results are fascinating. Only one, PPAR$\gamma$, was ever proposed as a candidate gene, with most having no known physiologic role in glucose homeostasis. Still, its easy to envision how they might act as several of the factors likely influence beta-cell development, insulin secretion, or proinsulin biosynthesis. And thats the second interesting finding, in that most of the identified genes seem to be involved in beta-cell biology as opposed to the insulin signaling or glucose transport systems. Finally, the greatest impact of any of these genes is quite modest – a 20% to 30% increase in diabetes risk – so we still have lots to learn about how these different genes interact to produce the profound diabetes susceptibility in certain families and ethnic groups. And one guesses more susceptibility genes will be found. So we have finally entered the genetic era, and its likely to be a very exciting time that finally may answer some of the tough questions in type 2 diabetes.

## ENVIRONMENT

The diabetes genotype causes a predisposition for glucose intolerance. The development of type 2 diabetes is influenced by environmental factors, some clearly defined, others less so. The Nurses Health Survey showed the expected positive associations between obesity and lack of physical activity in the development of type 2 diabetes, but also protection related to abstinence from smoking and to moderate alcohol use *(24)*. The protective effect of alcohol has been found in other studies, and was confirmed in a recent meta-analysis *(25)*. Also obscure is a reported association between type 2 diabetes and sleep deprivation *(26)*, and a protective effect of caffeine *(27)*. More understandable are the numerous studies showing associations between risk of type 2 diabetes and high calorie diets, physical inactivity, and our modern lifestyle in general.

These predisposing factors share an ability to negatively impact glucose homeostasis through worsening of insulin resistance or impairment of ß-cell function. Superimposing these factors onto a genetically compromised system augments the risk of hyperglycemia. The rapid emergence of these disadvantageous environmental factors is causing the worldwide diabetes epidemic. This concept was highlighted many years ago by nomadic or farm-based populations that moved to urban environments, followed by an explosion of diabetes, typically with profound obesity: Pima Indians in the Southwest United States, Saharan nomadic tribes, and Australian Aborigines are well-known examples. Studies that show reversal of the diabetes after members of these populations return to their prior way of life are particularly notable *(28)*. A recent example of the effect of population shifts is the rapidly rising incidence of type 2 diabetes in China and India as people flood to the cities; there is a 0.1–0.2% incidence of diabetes in rural parts of China as opposed to more than 5% for city dwellers. Perhaps the most distressing example of rapid change is the rising incidence of obesity in children in the US. As many as 20% of US children are now obese, and they are developing all of the elements of the metabolic syndrome: insulin resistance, hypertension, hyperlipidemia, and glucose intolerance *(29)*. Additionally gestational diabetes has doubled in prevalence in the U.S. over the last decade *(30)*.

An obvious conclusion is that a return to a healthier lifestyle should reverse the diabetes trend. Indeed, many studies have shown diet and exercise markedly decrease the onset of diabetes in persons with IGT *(2,31,32)*. The difficulty, of course, is trying to get people to change their habits. In addition, we are lacking long term studies of lifestyle modification in terms of a protective effect against cardiovascular disease.

## ACQUIRED ORGAN DYSFUNCTION

These refer to nongenetic defects in glucose homeostasis that occur as diabetes develops. This concept was first identified in studies that intensively treated glycemia in persons with type 2 diabetes, with resultant improvement in ß-cell function *(33)*. Later studies showed some reversal of insulin resistance. This effect is unrelated to the type of treatment used to lower the glucose level *(34)*, and is most effective early in the disease. Studies have shown long-term recovery of glucose tolerance in newly diagnosed patients with type 2 diabetes after a short-term insulin infusion or high dose sulfonylurea therapy *(35,36)*.

A particularly interesting study was performed in subjects with an average duration of 8 years of type 2 diabetes who were placed on an insulin pump for 3 weeks, attaining excellent glucose control *(37)*. The pump was stopped, and the subjects studied 2 days later, at which time large improvements in ß-cell function along with normalization of hepatic glucose production and some improvement in insulin resistance were seen. These three problems make up the classic triad of type 2 diabetes. A question posed at the beginning of this review is why patients invariably have this triad, when the organs involved lack a known physiological link. One answer is that, irrespective of the genetic and environmental factors in any given patient, as glucose intolerance develops the acquired organ abnormalities result in the "common phenotype" of the disease.

A substantial amount of research has focused on these acquired abnormalities, in particular ß-cell dysfunction. It was initially assumed the reversal of β-cell dysfunction noted above stemmed from the improvement in blood glucose level, and the term "glucose toxicity" was coined *(38,39)*. Supporting that idea were studies showing that experimental hyperglycemia in rodents invariably caused similar ß-cell dysfunction to that occurring in diabetic humans *(40)*, which was reversed by a glucose-lowering agent called phlorizin that restores normoglycemia by lowering the threshold for glucose clearance into urine, thus promoting glycosuria *(41)*. Many mechanisms for hyperglycemia-associated ß-cell dysfunction have been described from in vitro cell systems and animal models, and will be discussed later.

Also discussed later is a more recent suggestion that relates to another component of the diabetes phenotype, high circulating levels of triglycerides and fatty acids, as a cause of acquired organ abnormalities: so-called "lipotoxicity" *(42)*. There has also been interest in the combined effects of both elements, termed "glucolipotoxicity" *(43,44)*.

## INSULIN RESISTANCE VS BETA-CELL DYSFUNCTION

One of the most controversial issues during the 1980s and 1990s was whether insulin resistance or ß-cell dysfunction was the main cause of type 2 diabetes. The fact that persons with type 2 diabetes, and also those with IGT, invariably have both defects fueled the debate. Several highly discussed studies of people at presumed high-risk for type 2 diabetes, but still normoglycemic (high risk ethnic groups such as Pima Indians, those with both parents having type 2 diabetes, and women with prior gestational diabetes), attempted to identify the operative pathogenic elements before glucose values become abnormal. These studies generally reported that insulin resistance was present, but not ß-cell dysfunction *(45)*, resulting in a common belief at the time that insulin resistance was the earlier (and thus dominant) defect in this disease.

These conclusions were based on an experimental measure of ß-cell function that was later shown to be misinterpreted: the 2-hour insulin value postmeal or during an oral glucose tolerance test (OGTT). Insulin resistance was relatively easily measured, either by using the euglycemic glucose clamp, which is labor intensive and usually done with a limited number of subjects, or computer models that can be applied to large experimental groups. In contrast, the measurement of ß-cell function is highly complex. The insulin response to a meal normally is biphasic, with the amount released depending on many factors, such as the size and composition of the meal, prevailing glycemia, the subject's insulin sensitivity, etc. As glucose tolerance moves from normal to impaired, insulin release during the first 30 minutes of eating ("first phase") falls, and is absent by the time fasting glucose exceeds 115 mg/dL *(46)*. The later insulin secretion ("second phase") paradoxically becomes greater than normal in response to the hyperglycemia. The early studies concluded that the supernormal 2-hour insulin value, attributed to insulin resistance, proved that there was no ß-cell dysfunction at that stage. This misinterpretation was corrected by later studies that found reduced 30-minute and elevated 2-hour postmeal insulin values in IGT and early type 2 diabetes *(47)*, and others demonstrating that defective first phase insulin responses to intravenous glucose is a characteristic feature of type 2 diabetes *(48)*.

Investigators next turned to cross-sectional and natural history studies of ß-cell function versus insulin resistance. They confirmed that insulin resistance is already present when glucose values are within the normal glucose tolerance range *(49,50)*. There are a number of potential reasons: in some people this is presumably owing to a genetic abnormality that affects insulin sensitivity, and in others lifestyle factors, such as obesity, lack of exercise, high fat diets, aging, etc., may play a major role. Thereafter, insulin resistance is relatively unchanging. Therefore, a change in the degree of insulin resistance could not explain blood glucose values progressing from normal to IGT to diabetes. Instead, worsening ß-cell function is causative. These natural history studies observed a biphasic pattern: initial hyperinsulinemia, with blood glucose values maintained in the normal range or only mildly impaired, and, subsequently a falling insulin level ("β-cell failure"), resulting in rising glycemia *(49,50)*. Thus, the concept of type 2 diabetes began to change, with insulin resistance being an important risk factor for type 2 diabetes, but ß-cell function determining glycemia in persons genetically at risk for the disease.

The most recent studies have returned to the question of the priority of these abnormalities, in part reflecting better techniques to assess ß-cell function. One of the most used is the *disposition index*, based on the understanding that ß-cell function is dependent on the degree of insulin sensitivity. In other words, the insulin response to a meal or other stimulus is normally less in an insulin sensitive person such as a marathon runner than for a normoglycemic insulin resistant subject *(51)*. Thus, in normoglycemic subjects, insulin levels are more reflective of insulin sensitivity than ß-cell function. The relationship between experimentally measured insulin sensitivity and first phase insulin secretion as a measure of ß-cell function has been mapped out in a large number of normoglycemic subjects to derive the normal curve that is called the "disposition index" *(52,53)* (in Fig. 2, the hyperbolic curved lines are the experimentally derived normal curve). It is important to realize this is the normal system – everyone experiences insulin resistance at some time (puberty, pregnancy, aging), with most maintaining normoglycemia because of this ß-cell compensation. Indeed, many consider diabetes a failure of ß-cell compensation *(54)*. It is a commonly used research technique to plot where subjects with varying degrees of glucose tolerance fall on the disposition index to identify the relative roles of insulin resistance versus ß-cell dysfunction *(55)*.

A well-known study that used this method was performed in 48 normally glucose tolerant Pima Indians (a population with the highest worldwide incidence of type 2 diabetes), who were studied over an average of 5 years

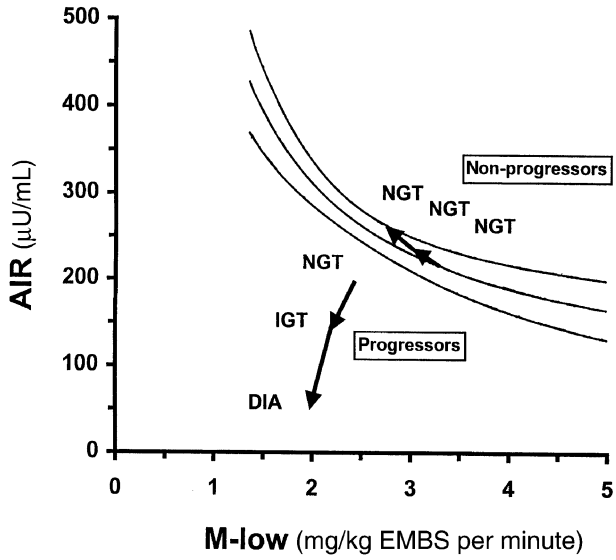


**Fig. 2.** Relationship between a measure of insulin sensitivity on the X axis and insulin secretion on the Y axis. The curved lines show the normal relationship among these parameters, which is termed the "disposition index." Forty-eight normal glucose tolerant Pima Indians were followed for 5 years, with 17 going on to develop type 2 diabetes (progressors) whereas 31 maintained normal glucose tolerance (nonprogressors). These findings reinforce key issues discussed in the text: ß-cell function is the major determinant of the blood glucose level in persons who are at risk for type 2 diabetes, and ß-cell dysfunction occurs before blood glucose values rise into the prediabetes range. From ref 56.

*(56)*. Seventeen developed type 2 diabetes (*progressors*) whereas 31 maintained normal glucose tolerance (*nonprogressors*). The groups were comparably obese and insulin resistant at the start of the study. Nonprogressors gained a little weight, and became a little more insulin resistant during the study, but stayed on the disposition curve, i.e., had perfect ß-cell compensation (Fig. 2). Progressors instead started below the insulin secretion part of the curve, and fell even further as their glycemia worsened, clearly showing that their deterioration in glucose tolerance resulted from worsening ß-cell function. It is particularly notable that the progressors started the study already off the normal curve, showing that despite their entering the study with glucose tolerance in the normal range, there was already subtle ß-cell dysfunction that had not yet resulted in a measured degree of glucose intolerance.

This latter concept has been observed in many other populations. One notable series of studies cross-sectionally examined Mexican-Americans and Caucasians across a wide range of glycemia from normal glucose tolerance to diabetes *(57,58)*. ß-cell function was determined as the insulin response to an OGTT that was adjusted for each subject's insulin sensitivity (based on glucose clamp testing) and 2-hour postmeal glucose values. ß-cell function was observed to fall as glycemia rose ever so slightly within the normal glucose tolerance range; subjects with 2-hour glucose values of 101–120 mg/dL had 60% lower adjusted mealtime insulin responses than those with 2-hour glucose values <100 mg/dL (normal glucose tolerance is defined by a 2-hour value of <140 mg/dL). Studies in other populations *(59,60)*, and a cross-sectional analysis of fasting glucose values *(61)*, had similar results.

Thus, it is now clear that insulin resistance and ß-cell dysfunction both precede measured defects in glucose tolerance. Defective ß-cell mass or function must be present for blood glucose values to rise even minimally above normal, given the precision of a healthy glucose homeostasis system. Therefore, the current definition of normal glucose tolerance is insensitive to early defects in glucose homeostasis. A recent study documented a several fold higher risk for type 2 diabetes with fasting blood glucose values at the high range of normal versus the low range ( >87 mg/dL vs <81 mg/dL), especially in the presence of obesity or hypertriglyceridemia *(62)*.

The question of which defect occurs first, and which is dominant, remains. One related long-standing argument is whether prolonged insulin resistance causes ß-cell failure through "exhaustion" (i.e., continued stimulation of otherwise normal ß-cells resulting in permanent dysfunction). The available facts do not support this proposal. Many morbidly obese highly insulin resistant subjects never develop diabetes. One thus assumes that it is necessary for the ß-cell compensatory ability to be compromised in some way for diabetes to develop. Stated another way, if one has healthy ß-cells, it appears to be virtually impossible to develop type 2 diabetes with the usual lifestyle and environmental influences. Thus, the key to a better understanding of type 2 diabetes is to define what constitutes "susceptible" ß-cells.

To summarize, both beta-cell dysfunction and insulin resistance occur long before blood glucose values reach prediabetes. One has not been shown to precede, or cause, the other. As such, type 2 diabetes is considered a "dual-defect disease" with both defects of equal importance *(63)*. However, it is unclear from this understanding whether early intervention for diabetes prevention would be most effective focusing on improving ß-cell function or insulin resistance. To date, the most effective treatment found for prevention of type 2 diabetes is diet and exercise *(2,31,32)*, which improves insulin sensitivity. Alternatively, viewing one defect as independent from the other may be overly simplistic, as ß-cell function and insulin resistance are linked by the disposition index. The best example of this is a series of studies of Hispanic women in Los Angeles with prior gestational diabetes (an extremely high risk group for type 2 diabetes) who were treated with the insulin sensitizers Troglitazone or Pioglitazone. Both drugs markedly decreased progression to permanent type 2 diabetes *(64,65)*. One might expect that the conclusion of these studies would highlight the importance of insulin resistance. Instead, the main reported benefit was prevention of ß-cell dysfunction as shown by sequential analysis of ß-cell function and insulin sensitivity, believed secondary to "ß-cell rest".

## β-CELL DYSFUNCTION IN TYPE 2 DIABETES

Studies over many years have described the ß-cell dysfunction in type 2 diabetes *(66)*. The major defects are:

1. Insulin is normally secreted in a pulsatile fashion, with oscillations every 11–14 minutes that provide for normal regulation of hepatic glucose production *(67,68)*. Also large bursts (termed ultradian oscillations) occur several times daily, especially after meals, and maximize nutrient clearance *(69)*. The pulsatile patterns are disrupted early in type 2 diabetes, with near-total elimination of the oscillations even in normoglycemic first degree relatives *(70,71)*.

2. An acute rise in glucose normally causes a burst of insulin secretion lasting 5–10 minutes ("first phase"), followed by another rise in insulin output lasting the duration of the hyperglycemic stimulus ("second phase"). The characteristic ß-cell defect in type 2 diabetes is loss of the first phase *(48,66)*, which occurs early in the course of the disease, with the first phase being reduced in half with fasting blood glucose levels above 100 mg/dL, and absent at values greater than 115 mg/dL *(46)*. The first phase serves an important role during food ingestion, to control the postmeal glycemic excursion. Selectively disrupting the first phase in healthy subjects causes glucose intolerance *(72,73)*, whereas restoring it in persons with type 2 diabetes markedly improves postprandial glycemia *(74)*. Importantly, Vague and Moulin *(75)* found a substantial recovery of the first phase following a period of intensive glucose control. As such, loss of first phase insulin secretion is the earliest identified aspect of the previously discussed acquired ß-cell defects. Furthermore, this defect provides a pathophysiological explanation for the transition from normal glucose tolerance to IGT.
3. As the disease progresses and hyperglycemia worsens over time, additional ß-cell defects occur. Indeed, a defining feature of type 2 diabetes is a relentless slow deterioration of ß-cell function that is blamed for the typical clinical course of eventual waning of responses to oral antidiabetic agents *(76)*. Also, this worsening explains why so many patients ultimately require insulin therapy for glucose control. These defects have been investigated almost exclusively in diabetic animals and cell systems. (A major obstacle to a better understanding of the ß-cell dysfunction is an inability to perform human pancreas biopsies because of risk of pancreatitis and/or leakage of digestive juices.) Animal studies have shown that there is a hierarchy of ß-cell defects at different glucose levels: modest hyperglycemia coexists with impaired glucose-induced insulin secretion that mimics human type 2 diabetes, and higher levels are associated with additional defects in proinsulin biosynthesis and ß-cell viability *(66)*.

## *Lowered β-Cell Mass In Type 2 Diabetes*

In addition to β-cell dysfunction, reduced ß-cell mass may also contribute to the development of type 2 diabetes. Measurement of ß-cell mass in humans is technically difficult and must be done on autopsy specimens; until recently, there were few studies, with a limited number of subjects. Furthermore, in many of these studies, controls were poorly matched. An increased ß-cell mass is part of the normal ß-cell compensation to insulin resistance. Weight-matching of control and diabetic subjects is now mandatory to minimize differences in insulin sensitivity, but was often not done in older studies. An important recent study by Butler et al of nearly 160 weight-matched control and type 2 diabetes subjects reported a 40–60% lowered ß-cell mass in this disease (Fig. 3) along with a 3-fold increase in ß-cell apoptosis *(77)*. Also, a recent study from Korea reported a large reduction in ß-cell mass in type 2 diabetic subjects, and also reported the novel finding that the mass of the glucagon-producing α-cells was increased *(78)*. Notwithstanding the limitations of the older studies, these studies confirmed the conclusion of most, but not all, prior work that ß-cell mass is lowered in type 2 diabetes.

The study by Butler et al *(77)* was the first study to provide data on subjects with IGT, finding a 40% reduced ß-cell mass. This novel observation is important for our understanding of the pathogenesis of type 2 diabetes. The sequence of events suggests that reduced β-cell mass may cause the earliest hyperglycemia, when the blood glucose begins to rise but is still within the normal glucose tolerance range, initiating in some way defective first phase insulin secretion. Postmeal glycemia then rises to a level defined as IGT, with the potential for more acquired defects, worsening of glycemia, and progression to diabetes. Although no additional human data exist, studies of partially pancreatectomized rats support that pattern. After a 60% pancreatectomy, rats normally compensate for the ß-cell loss through a combination of partial ß-cell regeneration and hyperfunction of the remaining ß-cells, and thus remain normoglycemic under normal circumstances. The partial ß-cell regeneration results in the ß-cell mass rising from 40% immediately after the surgery to 60% of normal, and remains at this level indefinitely. The ß-cell compensatory capacity of these rats to a minor dietary change was studied by adding some sugar (10%) to the water supply from which they drank freely *(79)*. Nonpancreatectomized rats given the sugar water drank it identically to the pancreatectomized rats. It is important to appreciate that the diet change was extremely modest: nonpancreatectomized rats given the sugar water over the 6 weeks of the study showed no obesity, hyperinsulinemia, or other metabolic difference compared to rats given tap water. In contrast, 60% pancreatectomy rats given sugar water developed mild hyperglycemia after a few weeks, with morning blood glucose values rising by 15 mg/dL. This small increase in glycemia was associated with a profound (75%) reduction in glucose-induced insulin secretion, analogous, it is proposed, to the process in humans that initiates progression to IGT and subsequent diabetes. Thus, one scenario for "susceptible ß-cells" is a reduced ß-cell mass

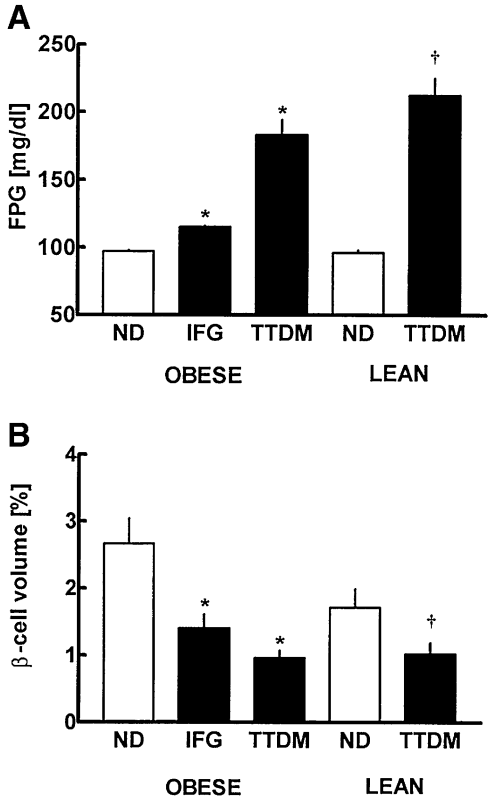


**Fig. 3.** Blood glucose values (top panel) and ß-cell volume (bottom panel) from a large number of autopsy specimens, with the data expressed by the absence or presence of obesity, and by the degree of glucose tolerance (no diabetes, impaired fasting glucose, type 2 diabetes mellitus). Note there is a 40% reduction of ß-cell volume in the subjects with impaired fasting glucose (IFG) and 40-60% reduction with type 2 diabetes. From ref 77.

that is incapable of maintaining normoglycemia when faced with environmental factors that have no detrimental metabolic effect when the ß-cell mass is normal.

Considerable current research is exploring the pathogenic basis for the lowered ß-cell mass in type 2 diabetes and prediabetes, with several proposed mechanisms:

1. Amyloid plaques occur in the islets of persons with type 2 diabetes, along with distorted and shrunken ß-cells *(80)*. The amyloid protein, *islet associated polypeptide* (IAPP), is a 37 amino-acid ß-cell-specific protein that is normally packaged in insulin granules and co-secreted with insulin *(81,82)*. The 25- to 28-amino acid sequence is the amyloidogenic portion. It is conserved in many species, all of which develop islet amyloid and diabetes. However, rodents lack the sequence, allowing the creation of transgenic mice that overexpress human IAPP to test the plausibility of IAPP-induced ß-cell destruction. Some, but not all, transgenic mice develop islet amyloid plaques with accelerated ß-cell apoptosis and diabetes *(83,84)*, engendering substantial interest in a pathogenic role for islet amyloid in type 2 diabetes *(85)*. Lorenzo et al *(86)* cocultured islets with exogenous IAPP, causing ß-cell death, which suggested that external amyloid plaques are cytotoxic. Also, this finding implied that amyloid deposition must be an end-stage part of the disease, not involved in the ß-cell reduction in IGT, as islet amyloid is not yet present in autopsy specimens from these subjects. The current view, however, has evolved to small intracellular microfibrils of IAPP being cytotoxic through mitochondrial damage or endoplasmic reticulum stress *(87,88)*, which is more in line with how other amyloid diseases, such as Alzheimer's, are thought to occur. In animal studies, microfibrils occur long before the extracellular amyloid plaques. Unfortunately, showing their presence in human autopsy tissue is an inexact science, and it remains unknown if they are present in IGT. Also, IAPP is normally produced and secreted. The cause of the microfibrils and large amyloid plaques in type 2 diabetes remains unknown. It is not related to the rate of IAPP secretion, as normally glucose tolerant obese subjects with long-term ß-cell compensatory hyperfunction for both insulin and IAPP lack islet amyloid at autopsy. Neither is it hyperglycemia *per se*, as amyloid plaques are often found in insulinomas *(89)*. Genetic mutations in IAPP have been sought, but

rarely found. Instead, the expectation is that mutations of other important proteins that normally keep IAPP soluble will be found, for example folding proteins, or others that prevent amyloid formation.
2. Pathological studies of ß-cells in type 2 diabetes have reported increased apoptosis as the cause of the lowered ß-cell mass *(77,90)*. Many mechanisms of cellular apoptosis are known: ER stress from misfolded proteins, oxidative stress, inflammatory mediators, glucolipotoxicity, etc. All are being studied for relevance to type 2 diabetes *(91–95)*.
3. There is no evidence to suggest that the cause of the lowered ß-cell mass is immune-mediated ß-cell destruction analogous to type 1 diabetes, as careful studies have shown the 2 types of diabetes are pathologically distinct.

## *Cellular Mechanisms of β-Cell Dysfunction*

There has been intense study of potential cellular mechanisms of the ß-cell dysfunction in type 2 diabetes. As already discussed, the inability to get islet tissue from free-living humans is a major impediment. Thus, with rare exceptions, these studies have been carried out in vitro using isolated islets from animals, clonal ß-cell lines exposed to high glucose and/or fatty acid levels, or by studying isolated islets from diabetic animals. There are a few studies of isolated islets from brain dead donors with type 2 diabetes *(17,90,96–99)*. Also, an emerging technique that holds considerable promise is laser capture microdissection to carve out islet-cells from pancreas slides of autopsy material, followed by mRNA amplification and expression profiling. Still, work with islet tissue from humans with type 2 diabetes is just beginning, and there remains a concern that islets obtained at the time of death (for any number of medical reasons) may be misleading in terms of the observed ß-cell physiology compared with the average otherwise healthy subject with type 2 diabetes. Thus current concepts of potential mechanisms are generally based on nonhuman systems. Several have been proposed *(66,100)*:

1. *Glucose toxicity*. This concept implies a direct effect of a high glucose level to impair one or more necessary aspects of ß-cell signaling, gene expression, cell architecture, etc, for normal insulin secretion. The list of reported ß-cell effects from experimental high glucose is lengthy; essentially every major ß-cell metabolic pathway, key enzyme, and important gene has been reported to be altered *(66)*. A variation on this concept is a series of papers performed in normal rats made hyperglycemic by glucose-infusion or partial pancreatectomy, showing a profoundly altered pattern of transcriptional expression of important ß-cell genes, termed "ß-cell dedifferentiation" *(101,102)*.
2. *ß-cell exhaustion:* This term implies an indirect effect of hyperglycemia to impair ß-cell function by way of the initial compensatory increase in insulin secretion depleting a key substance, metabolite, etc., below a crucial level that is required for continued insulin secretion. It is differentiated from glucose toxicity with an inhibitor of insulin secretion, such as diazoxide. Conceptually, with glucose toxicity, hyperglycemia, and consequently the ß-cell dysfunction, would worsen, but, with exhaustion, the "beta-cell rest" improves ß-cell function regardless of the blood glucose level. There is strong experimental support in both animal models and humans with type 2 diabetes for the exhaustion concept *(100,103–106)*.
3. *Impaired proinsulin biosynthesis:* Extensive in vitro data support a hyperglycemia-induced defect in proinsulin transcription *(107)*, although this requires high levels of glycemia *(101)* (i.e., this is one of the late-onset acquired ß-cell defects). Also, an added effect of excess fatty acids to impair proinsulin transcription, is potentially important *(108)*.
4. *Lipotoxicity:* There has been great interest in the concept that excess fatty acids are harmful to ß-cell function and viability, so-called lipotoxicity *(42)*. The working concept is that metabolic products of excess fatty acids, such as ceramides or other mediators of oxidative stress, cause ß-cell dysfunction and death *(94,109)*. However, this idea remains controversial, in part because the cellular systems and animal models used to study the subject are often so extreme that the relevance to human type 2 diabetes is unclear. Using in vitro culture of rat islets with high levels of fatty acids, Liu et al found no insulin secretory dysfunction or ß-cell death. Instead, they identified a system in normal ß-cells that protects against fatty acid-induced reductions in glucose metabolism that occur in other tissues (so-called "Randle effect"). In those tissues, excess fatty acids impair the activation of pyruvate dehydrogenase and retard glucose oxidation. In contrast, a relatively specialized feature of ß-cells is the high expression of a second pyruvate metabolism enzyme (pyruvate carboxylase), that allows the block in pyruvate metabolism to be bypassed *(110)*. Furthermore, pyruvate carboxylase is the entry step to mitochondrial metabolic pathways in ß-cells that are believed to be important signals for glucose-induced insulin secretion *(111)*. Therefore, Leahy and his collaborators have proposed that the heightened flow through pyruvate carboxylase not only protects against the detrimental effect of the excess fatty acids on glucose metabolism, but also provides a mechanism for the compensatory increase in insulin secretion that normally accompanies insulin resistance. Subsequent studies in a normoglycemic, insulin resistant rat model, Zucker fatty rats, support this theory *(112,113)*. Thus, excess fatty acids, in concert with normoglycemia, appear to augment ß-cell function, whereas excess fatty acids in the setting of hyperglycemia

impair ß-cell function, so-called *glucolipotoxicity (43,44)*. This theory shares with the lipotoxicity hypothesis the concept that excess production of fatty acid metabolites such as ceramides causes ß-cell dysfunction and death. However, in this concept a high glucose level must be present, as an increased level of the mitochondrial metabolic product of glucose, malonyl-CoA, is needed to inhibit fatty acid oxidation. Otherwise, the excess fatty acids would be oxidized, and thus detoxified. This combined hypothesis is particularly attractive, as it explains the compensatory β-cell hyperfunction of insulin resistance without diabetes (as occurs in obese people who are normoglycemic) and the toxic effect of the same level of hyperlipidemia in type 2 diabetes.

5. *Impaired incretin effect:* Incretin hormones are gut peptides that are released with eating and have a multitude of effects, including stimulating both the secretion and biosynthesis of insulin *(114–116)*. The best known are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). A characteristic feature of type 2 diabetes is a reduced incretin effect through 2 known mechanisms. The first is a lowered insulinotropic effectiveness of GIP *(117)*. The time of onset of this change is unclear, as it is present in some nondiabetic first-degree relatives of persons with type 2 diabetes *(118)*, but not women with a history of gestational diabetes *(119)*. The mechanism is not known, although one proposal is defective expression of GIP receptors on ß-cells *(120)*. In contrast, sensitivity to GLP-1 is mainly intact in type 2 diabetes *(117)*. However, a second mechanism for defective incretin regulation in type 2 diabetes is a decrease in the secretion of GLP-1 *(121)*. As yet, the molecular mechanisms for both of these observations, when they first occur, and their importance to the ß-cell dysfunction of type 2 diabetes, have not been determined.

## INSULIN RESISTANCE IN TYPE 2 DIABETES

Insulin resistance is literally a lowered sensitivity/responsiveness of a tissue or multiple tissues to insulin. However, in the context of type 2 diabetes, it is defined as impaired insulin-mediated glucose clearance into skeletal muscle, usually (but not always) with dysregulation of hepatic glucose production by insulin. This is because early studies showed dual effects of the insulin response to a meal for control of postmeal glycemia: activation of glucose transport into skeletal muscle, which is the major site of insulin-mediated clearance of a glucose load, and deactivation of hepatic glucose production. Both of these effects are impaired in type 2 diabetes, which explains how the term was first applied. This does not imply that insulin signaling in other tissues is intact. In the last decade, the intracellular signaling cascade that is downstream from the insulin receptor has, to a large degree, been mapped. Unexpectedly, this cascade is present in tissues other than the classic insulin-regulated end-organs, such as islet ß-cells, endothelial cells, neurons, etc. In addition, tissue specific knockout mouse studies have confirmed the presence of important physiologic effects of insulin in these tissues, with speculation that hyperglycemia causes dysregulation. However, the term "insulin resistance" still typically focuses only on muscle and liver, with endothelial dysfunction increasingly being added because of the presumed link between insulin resistance and cardiovascular disease in type 2 diabetes.

Simplistically, in the fasting state, the degree of hyperglycemia is directly determined by the rate of glucose overproduction by the liver. With eating, failure of adequate insulin-mediated nutrient-clearance into skeletal muscle combined with an attenuated deactivation of hepatic glucose production causes postprandial hyperglycemia *(122)*.

Recent investigation has focused on defining the cellular defects, aided by powerful new technologies, including glucose clamping with muscle biopsies, NMR analysis of cellular metabolic pathways, genetic mapping of target and novel mutations, and knockout mouse models (often tissue specific) for most of the key enzymes and transcription factors in the intracellular insulin action cascade. The major defect in muscle is impaired glucose transport into the cell combined with defective storage as glycogen *(123)*. Initially, it was assumed that genetic defects would be discovered in the glucose transport machinery, the insulin receptor, or its downstream signaling cascade. This has not been the case. Instead, current hypotheses mainly focus on disruption of the cellular insulin signaling cascade by external factors. Several mechanisms are under investigation:

1. *Serine phosphorylation of IRS-1*. IRS-1 (Insulin Receptor Substrate-1, a component of the insulin signaling cascade that is immediately downstream from the insulin receptor) plays a key role in insulin signaling in skeletal muscle. The insulin signal propagates from the insulin receptor through IRS-1 to the distal signaling peptides, mainly through phosphorylation of tyrosines. Normoglycemic relatives of persons with type 2 diabetes have decreased insulin-stimulated IRS-1 tyrosine phosphorylation *(124)*. A potential explanation relates to the recent finding that serine phosphorylation of IRS-1 attenuates insulin signaling, perhaps normally to turn off the insulin response, and

that states of insulin resistance are characterized by enhanced serine phosphorylation of IRS-1 *(125–128)*. Another idea is that degradation of IRS-1 is accelerated *(129)*.

2. *Excess glucosamine*: Glucose is mainly metabolized through glycolysis, but a small percentage forms UDP-acetylglucosamine. Increased flux through this pathway has been shown to impair insulin-mediated glucose transport in adipocytes *(130)*. Subsequent studies in mice whose livers overexpress the hexosamine biosynthesis enzyme, fructose-6-phosphate amidotransferase, showed enhanced glycogen storage and the metabolic syndrome (obesity, hyperlipidemia, and, glucose intolerance) *(131)*, and rats fed glucosamine developed skeletal muscle insulin resistance *(132)*. It is currently thought that this system normally acts as a cellular nutrient sensor, but goes awry when flux is excessive *(133)*. At present, it remains unclear what role this pathway plays in human type 2 diabetes *(134)*.
3. *Defective mitochondria:* There is great interest in mitochondrial dysfunction as a cause of skeletal muscle insulin resistance. This was highlighted in an important study that used state of the art NMR technology to examine normal weight, normoglycemic, insulin resistant offspring of parents with type 2 diabetes, finding defective skeletal muscle mitochondrial function *(135)*. Increased storage of triglyceride in muscle and liver has recently been proposed to be a marker of insulin resistance *(136,137)*. Petersen et al have speculated that mitochondrial dysfunction explains both the excess triglyceride accumulation and the defective glucose uptake that characterize muscle-related insulin resistance in type 2 diabetes because of decreased fatty acid oxidation and ATP production *(135)*. Additional findings that support mitochondrial dysfunction are more type IIb muscle fibers (nonoxidative type) in persons with type 2 diabetes *(138)*, and a reduced function and number of skeletal muscle mitochondria *(139)* that improved in tandem with an increased insulin sensitivity after weight loss and dietary therapy *(140)*.
4. *Fatty acid-induced insulin resistance and a role for inflammation*. As discussed earlier, another aspect of the diabetes phenotype is hyperlipidemia. There is now strong experimental support for insulin resistance-inducing effects of excess fatty acids from both lipid infusion studies in healthy man and in vitro studies *(141–144)*. It was initially assumed that the mechanism was a competition between fatty acids and glucose oxidation (the Randle cycle), but a much more complex effect of fatty acids on insulin signaling has evolved. Considerable evidence now supports fatty acids interfering with insulin signaling through a cascade of effects that includes protein kinase C (PKC)-induced serine phosphorylation of IRS-1 (PKC-theta knockout mice are resistant to fat-induced insulin resistance *(145)*), the proinflammatory mediators c-Jun N-terminal kinase (JNK) and IkappaB/NfkappaB *(146)*, and suppressor of cytokine signaling 3(SOCS-3), which impairs insulin signaling at several sites *(147)*. High dose aspirin ameliorates insulin resistance in animals by interfering with IkappaB kinase beta (IKKbeta) *(148)*, and multicenter human trials to test that effect are underway.
5. *Alternate fatty acid effects*. Other aspects of lipotoxicity-induced insulin resistance are being investigated, including induction of oxidative stress *(95)* and malonyl-CoA-induced alterations in AMP kinase *(149)*. The latter is proposed to be a site of action of the oral agent metformin *(150)*.
6. *Altered adipokine regulation.* The last decade has seen the discovery that adipose tissue is far more complex than simply acting as a storage site for triglyceride. Adipocytes are now known to produce many proteins (cytokines and adipokines) that have effects on a number of tissues, including skeletal muscle and liver, and concurrently on insulin sensitivity *(151)*. Of particular interest regarding the effect on skeletal muscle are TNFα *(152)* and adiponectin *(153–155)*, as well as the recently described retinol binding protein 4 *(156)*. Another adipocyte-related factor of current interest is resistin, which was initially linked to the insulin resistance of obesity and diabetes *(157)*. Subsequently its pathological role has been questioned *(158)*. However, interest in resistin has returned, as resistin null mice have been shown to become hypoglycemic during fasting, and are protected against glucose intolerance and insulin resistance during fat feeding, confirming a physiologic effect *(159)*. This study localized the action of resistin to the liver, showing that it de-activates AMP-kinase, impairing transcriptional regulation of gluconeogenic enzymes. Subsequent studies using knockout mice, transgenic resistin overexpressing mice, adenoviral overexpression systems, interfering RNA, etc. confirmed and expanded this hypothesis *(160–162)*. The results unequivocally show that resistin has an important regulatory role over hepatic glucose production in health and disease, at least in rodents. However, the role of resistin has not yet been elucidated in humans.

## SUMMARY

The pathological sequence for type 2 diabetes shown in Fig. 1 entails many elements. A genetic predisposition appears to be mandatory, and specific predisposition genes are just beginning to be understood. The diabetes phenotype is then influenced by many environmental factors that share an ability to stress the glucose homeostasis system, either by causing or worsening insulin resistance, or by impairing insulin secretion. Decreased ß-cell mass through genetic or cytotoxic factors is a predisposing factor for glucose intolerance, and may be an explanation

for "susceptible" ß-cells in this disease. Without these predisposing features, the glucose homeostasis system is amazingly adept at maintaining normoglycemia despite poor lifestyle practices. Alternatively, if the blood glucose level rises even a small amount above normal, acquired defects in the glucose homeostasis system occur. Early on, the control of mealtime glycemia is impaired through a reduction in first phase insulin secretion. As the blood glucose rises even more, perhaps in concert with the excess fatty acids that are a typical feature of obesity and insulin resistance, ß-cell function deteriorates even further, along with a modest decline in muscle insulin sensitivity and the onset of exaggerated hepatic glucose production. Blood glucose levels then rise to full blown diabetes. This review has presented multiple proposed signaling abnormalities or other pathological processes for the ß-cell dysfunction and insulin resistance in type 2 diabetes. None are fully accepted, nor is it likely that a single defect will explain the ß-cell dysfunction/death or insulin resistance in this complex disease. Further, it is difficult to understand how cell-based and animal-derived defects relate to humans with type 2 diabetes. Regardless, we can look forward in the next several years to further analysis of the current, as well as new, hypotheses to explain the pathogenesis of type 2 diabetes.

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# 3 Metabolic Mechanisms of Muscle Insulin Resistance

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***CONTENTS***



**Summary**

Obesity has emerged as one of the leading global health threats of the 21st century. The current worldwide pandemic has been triggered by lifestyle habits that promote overconsumption of energy rich foods while also discouraging routine physical activity. These environmental factors impose a chronic energy imbalance that leads to a steady gain of body fat and a constellation of accompanying metabolic abnormalities. As adiposity increases, so does the risk of developing insulin resistance and type 2 diabetes, evidenced by the fact that over 80% of type 2 diabetic pateints are obese. Skeletal muscle is a primary target tissue of these disorders and a progressive loss of muscle insulin sensitivity contributes to deteriorating glucose control. Compelling evidence suggests that the development of skeletal muscle insulin resistance is intimately associated with systemic dyslipidemia and intramuscular lipid accumulation. Conversely, the antidiabetic effects of exercise coincide with marked improvements in lipid homeostasis, both systemically and locally. These findings have inspired a new area of metabolic research centered on the concept of "lipotoxicity" and the goal of understanding the molecular mechanisms that link chronic lipid oversupply to tissue dysfunction and the onset of disease. This chapter provides an overview of recent advances in this area, placing emphasis on lipid-induced functional impairments in skeletal muscle and new perspectives on the pathophysiology that drives insulin resistance.

**Key Words:** Diabetes; fat oxidation; insulin action; lipids; metabolic profiling; mitochondria; skeletal muscle; exercise; peroxisome proliferator activated receptors.

## INTRODUCTION

For most of human evolution, the ability to store nutrients in the form of esterified lipids [triacylglycerols (TAG)] has constituted a survival advantage for times of famine and/or energy deficit. In more recent times, this "thrifty" fuel economy has been challenged by overconsumption of energy-dense foods and reduced physical activity, leading to dysfunction of major tissues and organs and alarming increases in the incidence of obesity-related diseases such as diabetes, hypertension, and cardiovascular disease. Skeletal muscle has received particular attention, because it is the major site of glucose disposal, accounting for approx 80% of glucose clearance in the postprandial state. With the recent advent and integration of tools of molecular biology and comprehensive

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metabolic analysis, a review of mechanisms by which overconsumption of energy rich diets leads to insulin resistance in skeletal muscle seems warranted. Particular themes that will be highlighted in this chapter include: 1) Inter-organ communication networks among liver, adipose tissue, and muscle that contribute to muscle insulin resistance; 2) Critical evaluation of the idea that lipid-induced muscle insulin resistance occurs as a consequence of reduced fatty acid oxidation, leading to accumulation of toxic lipid-derived metabolites and TAG; 3) Discussion of an alternative and recently emergent concept that accumulation of lipid-derived metabolites that interfere with insulin action occurs due to an increase rather than a decrease in fatty acid oxidation in skeletal muscle.

## INTER-ORGAN COMMUNICATION AND DEVELOPMENT OF MUSCLE INSULIN RESISTANCE

Ingestion of high fat diets and development of obesity is associated with increased triglyceride storage at sites other than adipose tissue, including skeletal muscle, the heart, kidney, and liver. These changes are often associated with chronic elevations in circulating free fatty acids and TAG. This has led to the widely accepted notion that obesity-associated tissue dysfunction, including insulin resistance and cell death, is a direct consequence of chronic exposure of tissues to elevated lipids and resultant accumulation of toxic by-products of lipid metabolism. Whereas much evidence continues to support this concept, as will be highlighted in later sections of this chapter, recent work suggests the presence of other, more indirect pathways for development of muscle insulin resistance driven by events in distant tissues such as liver and adipose.

Once considered a passive energy reservoir, adipose tissue is now recognized as an important endocrine organ that informs the brain and peripheral tissues of changes in whole-body energy status. The endocrine function of the adipocyte came to light with the hallmark discovery of leptin as the mutated gene in homozygous *ob/ob* mice, which exhibit an obesity syndrome characterized by severe adiposity, hyperphagia, hyperlipidemia, hyperinsulinemia, and insulin resistance in multiple tissues, including skeletal muscle (1; 2). Leptin replacement in *ob/ob* mice restores energy balance by acting on central and peripheral receptors that mediate changes in feeding behavior and systemic fuel metabolism (1; 2). The ensuing decade of research has revealed that adipose cells also produce a variety of other hormones and cytokines (referred to collectively as "adipokines"). These include peptide hormones such as adiponectin (also Acrp30) and resistin, and proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor α (TNFα). Many of these adipocyte-secreted peptides regulate both lipid and glucose metabolism *(3)*, and as result, may play a direct role in development of insulin resistance and diabetes *(4–6)*. For example, the two best-characterized antidiabetic adipokines, leptin and adiponectin, have been shown to decrease triglyceride synthesis, promote fatty acid catabolism, and enhance insulin action in both skeletal muscle and the liver. Although information on the signaling mechanisms that mediate these actions is still unfolding, growing evidence indicates that both leptin and adiponectin cause activation of 5′ AMP kinase, an enzyme that normally mediates responses to conditions of energy deficit (sensed as a fall in ATP and a rise in AMP levels) by activating fatty acid oxidation. Interestingly, leptin levels are increased, and adiponectin levels are decreased in insulin resistant, obese human subjects and animal models, suggesting that obesity leads to a state of leptin resistance, and one of adiponectin deficiency. In addition to perturbations relating to leptin and adiponectin, insulin resistance is associated with increased production of resistin, IL-6, TNFα, and retinol-binding protein 4 (RBP-4) by adipose tissue, all of which have been shown to induce insulin resistance in both muscle and the liver *(4,7–9)*.

Also consistent with a critical role of adipose tissue in control of metabolic function in muscle and other peripheral tissues are the effects of lipoatrophy. For example, several strains of transgenic mice have been created with ablation or loss of function of white adipose tissue *(10–12)*. Animals lacking white adipose tissue have severe hepatic and muscle insulin resistance, occurring in concert with large increases in triglyceride stores in both tissues *(13)*. Moreover, transplantation of normal fat tissue into such mice restores insulin sensitivity *(14)*, which appears to be mediated by redistribution of fat from the liver and muscle to the adipose depot and via endocrine factors produced by the transplanted fat tissue. Most evidence points to leptin as the key endocrine mediator in these studies. Thus, leptin infusion ameliorates insulin resistance in lipoatrophic mice *(15,16)*, whereas transplantation of fat from leptin-deficient mice into such animals fails to improve insulin sensitivity *(17)*.

Furthermore, leptin administration to humans with severe lipodystrophy partially reverses their severe insulin resistance and hyperlipidemia *(18)*.

Expression of the insulin-regulated glucose transporter 4 (GLUT-4) is strongly depressed in adipose tissue but is much less reduced in skeletal muscle in animals and humans with type 2 diabetes *(19)*. Because skeletal muscle accounts for approx 80% of glucose disposal in the postprandial state, the diabetes-associated reduction in adipose GLUT-4 did not at first seem highly relevant to metabolic dysregulation. However, subsequent studies showed that mice with adipose-specific knockout of GLUT-4 have impaired insulin sensitivity in muscle and liver *(19)*. The impairment in insulin action is only apparent in tissues in situ and not in excised tissue samples, implying participation of a blood-borne hormone or metabolite that mediates the effect. A subsequent study has demonstrated that mice deficient in adipose GLUT-4 have elevated levels of RBP-4 in blood, due in part to increased production of the hormone by adipose tissue. Furthermore, increases in circulating RBP-4 levels in normal mice induced by infusion or transgenic expression causes insulin resistance *(9)*. Interestingly, food deprivation (fasting) also causes a form of insulin resistance and is associated with a decrease in adipose GLUT-4 expression *(20)*. This raises the possibility that the original purpose of adipocyte-derived insulin-desensitizing molecules, such as RBP-4, TNFα and resistin, may have been to prevent hypoglycemia in the fasted state, which with the advent of overnutrition and senescence in modern life has been subverted to create pathophysiology *(21)*.

Alterations in metabolic function in liver can also lead to changes in insulin sensitivity in muscle, constituting a second inter-organ signaling network. For example, in rats fed a high-fat diet, hepatic expression of malonyl-CoA decarboxylase (MCD) causes near-complete reversal of severe muscle insulin resistance *(22)*. MCD affects lipid partitioning by degrading malonyl-CoA to acetyl-CoA, thereby relieving inhibition of carnitine palmitoyl transferase-1 (CPT1), the enzyme that regulates entry of long-chain fatty acyl-CoAs (LC-CoAs) into the mitochondria for fatty acid oxidation. In addition, malonyl-CoA is the immediate precursor for de novo lipogenesis. To gain insight into lipid-derived metabolites that might participate in the cross talk between the liver and muscle in the regulation of insulin sensitivity, metabolic profiling of 36 acyl-carnitine species was performed in muscle extracts by tandem mass spectrometry. These studies revealed a unique decrease in the concentration of one lipid-derived metabolite, β-OH-butyrylcarnitine, in muscle of MCD-overexpressing animals that likely resulted from a change in intramuscular β-oxidation and/or ketone metabolism *(22)*. Our current interpretation of the mechanistic significance of these findings is elaborated further below. Another example of the profound effects of altered lipid partitioning in control of whole-animal metabolic status comes from studies of animals deficient in stearoyl-CoA desaturase-1 (SCD-1) activity in liver. This enzyme catalyzes the conversion of saturated fatty acids (e.g., C16:0, C18:0) to monounsaturated fatty acids (C16:1, C18:1). Knockout of SCD-1 in ob/ob mice reverses obesity and insulin resistance in these animals *(23,24)*. This effect appears to be mediated by enhanced rates of oxidation of saturated versus unsaturated LC-CoAs. There is also evidence to suggest that SCD-1 deficiency results in increased AMPK activity, which further enhances overall rates of fatty acid oxidation *(25)*. Conversely, human studies have shown that high expression and activity of SCD-1 in skeletal muscle of obese subjects contributes to decreased AMPK activity, reduced fat oxidation and increased TAG synthesis *(26)*.

Finally, there is growing evidence that adipose tissue and the liver play important roles in the regulation of insulin sensitivity via inflammatory mechanisms *(27)*. At high doses, salicylates (aspirin) reverse insulin resistance and hyperlipidemia in obese rodents while suppressing activation of the NF-κB transcription factor *(28,29)*. Subsequently, it has been demonstrated that high-fat diets or obesity result in activation of NF-κB and its transcriptional targets in the liver. Overexpression of a constitutively active version of the NF-κB activating kinase, IkB kinase catalytic subunit β (IKK-β) in liver of normal rodents to a level designed to mimic the effects of high-fat feeding results in liver and muscle insulin resistance and diabetes *(8)*. In addition, both high-fat feeding and IKK-β overexpression increase expression of proinflammatory cytokines such as IL-6, IL-1β, and TNFα in the liver, and lead to increased levels of these molecules in blood. Antibody-mediated neutralization of IL-6 in these models partially restores insulin sensitivity *(8)*. Interestingly, mice with IKK-β knockout in the liver are protected from diet-induced impairment of hepatic insulin action but still develop muscle and adipose insulin resistance *(30)*. In contrast, mice with IKK-β knockout in myeloid cells are protected against diet-induced insulin resistance in all tissues *(30)*. These findings suggest the primary mediator of the inflammatory response to elevated lipids may be macrophages that reside within the liver and adipose depots.

How is metabolic fuel overload linked to activation of stress pathways and cytokine production in liver and adipose tissue (or within liver- and adipose-associated immune cells), that leads in turn to development of muscle insulin resistance? One intriguing possibility is that excess lipids may trigger stress responses in the endoplasmic reticulum (ER) *(31)*. Thus, markers of ER stress are elevated in the liver and adipose tissue of genetic or diet-induced forms of obesity, and this in turn is linked to activation of the c-jun amino-terminal kinases (JNK), which are known to interfere with insulin signaling via serine phosphorylation of insulin receptor substrate-1. Moreover, genetic manipulations that relieve ER stress also confer resistance against diet-induced metabolic dysfunction. The question of whether obesity-induced disturbances in ER function stem from chronic lipid overload, the anabolic pressures of hyperinsulinemia, cytokine-induced signaling, mitochondrial dysfunction, and/or other pathophysiological assaults now awaits further investigation. In this regard, it is interesting to note that several of the enzymes responsible for processing excess lipid (e.g., enzymes of lipid esterification) are integral membrane proteins that reside in the ER.

## METABOLIC ADAPTATIONS LEADING TO INSULIN RESISTANCE IN MUSCLE—A PROBLEM OF IMPAIRED OR INCREASED FATTY ACID OXIDATION?

The foregoing sections highlight the important role played by liver and adipose tissue in regulation of muscle insulin sensitivity via two major mechanisms: 1) alteration of fuel delivery to muscle; 2) production of hormones and inflammatory mediators. The remainder of this chapter will focus on key metabolic changes that occur in muscle in response to chronic exposure to elevated concentrations of metabolic fuels, particularly circulating lipids, and how these may contribute to development of muscle insulin resistance. This will include a discussion of the roles of key transcription factors and metabolic regulatory genes in mediating these adaptive changes. We will begin by describing obesity-related changes in intermediary metabolism in skeletal muscle.

Fatty acids and glucose constitute the primary oxidative fuels that support skeletal muscle contractile activity, and their relative utilization can be adjusted to match energy supply and demand. Metabolic fuel "switching" is mediated in part by the ability of lipid and carbohydrate catabolic pathways to regulate each other. The idea that elevated fatty acid oxidation inhibits glycolysis and glucose oxidation was first presented in 1963 as the "glucose-fatty acid cycle" *(32)*. Principal elements of this model hold that (*a*) provision of lipid fuels (fatty acids or ketones) promotes fatty acid oxidation and inhibits glucose metabolism; (*b*) the inhibitory effects of lipid fuels on glucose oxidation are mediated via inhibition of hexokinase, phosphofructokinase, and pyruvate dehydrogenase. It has further been suggested that these lipid-induced changes in metabolic regulation lead to diminished insulin-stimulated glucose transport *(33)*. Conversely, high glucose concentrations suppress fatty acid oxidation via malonyl-CoA-mediated inhibition of the key enzyme of fatty acid oxidation, CPT1 *(34)*. This pathway represents a near-exact complement to the glucose-fatty acid cycle and is sometimes referred to as the "reverse glucose-fatty acid cycle."

In more recent years the CPT1-malonyl-CoA "partnership" has been featured as a key constituent of the lipotoxicity paradigm *(35)*, in which elevated levels of malonyl-CoA and impaired fatty acid catabolism are thought to encourage cytosolic accumulation of "toxic" lipid species that disrupt insulin signaling and glucose disposal in muscle. Consistent with this notion, muscle malonyl-CoA concentrations are elevated in several (but not all) models of rodent obesity, and this has been linked with intramyocellular accumulation of LC-CoAs *(36,37)*. Furthermore, knockout mice lacking acetyl CoA carboxylase-2 (ACC2) have decreased muscle malonyl-CoA levels, increased β-oxidation, and are protected against diet-induced obesity and insulin resistance *(38)*.

It is well documented that with ingestion of high-fat diets and onset of obesity, TAG begin to be stored at sites other than adipose tissue, including skeletal muscle, heart, kidney, liver, and pancreatic islets. Because TAG are a relatively inert intracellular metabolite, attention has turned to other lipid-derived species as potential mediators of lipid-induced tissue dysfunction that often accompanies obesity, eventually leading to metabolic syndrome and type 2 diabetes. For example, insulin resistance in human muscle has been reported to be negatively associated with levels of long chain acyl CoAs *(39)*, and infusion of lipids or ingestion of high fat diets in rodents leads to accumulation of these metabolites in various tissues in concert with development of insulin resistance *(40)*. It has further been suggested that increased cellular fatty acyl CoA and diacylglycerol levels activate PKC-theta, leading in turn to phosphorylation of insulin receptor substrate-1 (IRS-1) on Ser 307 *(40)*. Phosphorylation at

Ser 307 impairs insulin receptor-mediated tyrosine phosphorylation of IRS-1, and as a consequence, interferes with insulin stimulation of IRS-1-associated PI3-kinase, leading to impaired phosphorylation and regulation of distal components of the pathway such as AKT-1 *(41–44)*. Interestingly, dramatic weight loss induced in morbidly obese subjects by bariatric surgery results in a striking improvement in insulin sensitivity, which is correlated with decreases in the levels of some, but not all long-chain acyl CoA species in skeletal muscle *(45)*. Metabolites that decreased included palmitoyl CoA (C16:0), stearoyl CoA (C18:0), and linoleoyl CoA (C18:2), whereas no significant decreases were observed for palmitoleoyl CoA (C16:1) or oleoyl CoA (C18:1).

Sphingolipids have also been implicated in a number of disease states and pathologies. Ceramide is viewed as the "hub" of sphingolipid metabolism, as it serves as the precursor for all complex sphingolipids, and as a product of their degradation *(46)*. Ingestion of high fat diets has been shown to result in accumulation of ceramides in various mammalian tissues, and these metabolites have been implicated in insulin resistance *(47,48)*. Thus, ceramide has been shown to accumulate in insulin-resistant muscles in both rodents and humans, and lipid infusion results in elevated ceramide levels in concert with decreasing insulin sensitivity. Moreover, exercise training, which increases insulin sensitivity, causes clear decreases in muscle ceramide levels *(49)*. When added to cultured adipocytes or myocytes, ceramide causes acute impairment of insulin-stimulated glucose uptake and GLUT4 translocation *(50,51)*. These effects appear to be mediated by effects of ceramide to inhibit tyrosine phosphorylation of IRS-1 and/or activation of Akt/protein kinase B *(47,48)*.

All of the foregoing observations would be consistent with a model in which glucose-induced increases in malonyl CoA levels in muscle would lead to reduced rates of fatty acid oxidation, and consequent accumulation of TAG, LC-CoA, diacylglycerol, and ceramides in muscle, possibly contributing to development of insulin resistance. However, in humans, the relationship between malonyl-CoA and insulin resistance is less clear. Although several laboratories have shown that muscle malonyl-CoA content increases in association with decreased fat oxidation during a hyperinsulinemic-euglycemic clamp *(52,53)*, basal levels of malonyl CoA were found to be similar in lean, obese, and type 2 diabetic subjects *(54)*. Moreover, fat oxidation rates during hyperinsulinemic conditions were actually increased in diabetic subjects compared to controls, despite similarly high levels of malonyl-CoA *(40,55)*. Thus, whereas the malonyl-CoA/CPT1 axis plays a key role in regulating muscle lipid oxidation, it is unclear whether disturbances in this system are an essential component of insulin resistance.

The broadly accepted idea that obesity-associated increases in malonyl-CoA antagonize fat oxidation, thereby causing insulin-desensitizing lipids to accumulate, seems at odds with the idea that insulin resistance stems from increased fatty acid oxidation in muscle (the Randle hypothesis) *(37,55)*. Adding further confusion, a survey of the literature reveals reports describing either increased or decreased muscle fat oxidation in association with obesity, thus seeming to support both possibilities. Perhaps neither is entirely correct or incorrect. To reconcile these discrepancies the concept of "metabolic inflexibility" has been proposed, holding that muscles from obese and insulin-resistant mammals lose their capacity to switch between glucose and lipid substrates *(56)*. In support of this idea, skeletal muscle fat oxidation in obese and type 2 diabetic subjects compared with lean subjects is greater in the postprandial state (simulated by hyperinsulinemic, euglycemic clamp) but depressed in the postabsorptive state *(57)*. Thus, whereas control subjects were able to adjust muscle substrate selection in response to a changing nutrient supply, the insulin-resistant subjects were not. In addition, increases in fatty acid oxidation that normally occur in response to fasting, exercise, or β-adrenergic stimulation are either absent or less apparent in obese and/or diabetic subjects *(58)*. Many of these metabolic adjustments are mediated at a transcriptional level. Thus, before returning to discuss a unifying theory of muscle insulin resistance that can potentially reconcile the debate about how "toxic" lipid-derived metabolites accumulate in muscle, we will first summarize the role of key transcription factors in metabolic adaptation to overnutrition.

## TRANSCRIPTION-BASED MECHANISMS OF METABOLIC REPROGRAMMING IN MUSCLE IN RESPONSE TO OVERNUTRITION

Understanding of metabolic reprogramming and fuel selection in skeletal muscle under different physiological conditions has deepened as a result of new knowledge about transcription factors that serve as broad metabolic regulators. For example, the family of peroxisome proliferator-activated receptors (PPARs) are powerful global regulators of metabolism according to nutritional status *(59–61)*. The three major PPAR subtypes, PPARα, δ,

and γ have distinct tissue distributions that reflect their discrete but overlapping functions. PPARα is expressed most abundantly in skeletal muscle, the heart, and the liver, where it plays a key role in regulating pathways of β-oxidation *(61)*. Although PPARγ, the target of the insulin-sensitizing thiazolidinediones, is expressed primarily in adipose tissue *(62)*, recent studies have demonstrated that muscle-specific deletion of PPARγ in mice resulted in whole-body insulin resistance, suggesting the low levels of this receptor in muscle are physiologically important *(63)*. PPARδ, the most ubiquitous and least characterized of these receptors, has been shown to regulate both fatty acid oxidation and cholesterol efflux, apparently sharing many duties with PPARα *(60,64)*. Recent findings also suggest that PPARδ participates in the adaptive metabolic and histologic (fiber-type switching) response of skeletal muscle to endurance exercise *(65)*.

Pharmacological activation of either PPARα or PPARδ results in the robust induction of genes that influence lipid metabolism, including several associated with lipid trafficking, interorgan lipid transport and cholesterol efflux, fatty acid oxidation, glucose sparing and uncoupling proteins (UCPs) *(60,64)*. Interestingly, a similar set of genes is upregulated by diverse circumstances that raise circulating free fatty acids, including obesity, diabetes, overnight starvation, high-fat feeding, and acute exercise *(60,64,66)*. Studies in PPARα-null mice indicate that this nuclear receptor is essential for regulating both constitutive and inducible expression of genes involved in fatty acid oxidation in the liver and heart *(61)*. However, skeletal muscles from PPARα-null mice are remarkably unperturbed with regard to lipid metabolism, and retain their ability to upregulate several known PPAR-target genes in response to starvation and exercise, perhaps owing to functional redundancy between PPARα and PPARδ *(60,64)*.

The nutritionally responsive PPAR receptors are themselves regulated by interactions with a variety of co-activators and corepressors. Promiment among these in terms of regulation of skeletal muscle physiology are the PPARγ Coactivator-1 (PGC-1) proteins, PGC-1α and PGC-1β. PGC1α was originally identified as a PPARγ interacting protein responsible for regulating mitochondrial replication in brown fat *(67)*. Subsequent studies identified a second isoform (PGC1β) and determined that both proteins are widely expressed and function as promiscuous coactivators of a number of nuclear hormone receptors, as well as other kinds of transcription factors *(68)*. In addition to its interactions with PPARs to regulate lipid metabolism, PGC1α stimulates mitochondrial biogenesis via coactivation of the nuclear respiratory factor *(69)* and regulates genes involved in oxidative phosphorylation through interactions with estrogen-related receptor α *(70)* in muscle. PGC1α also coactivates myocyte enhancer factor-2 *(69)*, a muscle-specific transcription factor involved in fiber-type programming. PGC1α is more abundant in red/oxidative muscle and is induced by exercise, whereas its expression is decreased both by inactivity and chronic high-fat feeding *(71,72)*. In contrast, PGC1β mRNA levels are unaltered by these manipulations.

## UPREGULATION OF FATTY ACID OXIDATION AS A MECHANISM FOR GENERATING LIPID SPECIES THAT IMPAIR INSULIN ACTION—A UNIFYING HYPOTHESIS?

We now return to the issue of how the seemingly discrepant hypotheses of obesity-related muscle insulin resistance (a condition of up-regulated or down-regulated fatty acid oxidation?) can be reconciled. One emergent idea is that lipid-induced upregulation of the enzymatic machinery for β-oxidation of fatty acids is not coordinated with downstream metabolic pathways such as the tricarboxylic acid (TCA) cycle and electron transport chain *(71,73)*. This idea came to light via the observation that isolated mitochondria from rats fed on a high-fat diet had the same rate of [$^{14}$C] palmitate oxidation to $CO_2$ as mitochondria isolated from muscles of standard chow-fed control rats, but with a larger accumulation of radiolabeled intermediates in an acid-soluble pool *(71)* (Fig. 1A, B). This suggests that insulin resistant muscles from fat-fed rats have a higher rate of "incomplete" fatty acid oxidation. Consistent with this idea is the previously discussed study in which hepatic expression of malonyl-CoA decarboxylase (MCD) caused near-complete reversal of severe muscle insulin resistance in rats fed a high-fat diet *(22)*. In this study, metabolic profiling of 36 acyl-carnitine species by tandem mass spectrometry revealed a unique decrease in the concentration of one lipid-derived metabolite, β-OH-butyrylcarnitine (C4-OH), in muscle of MCD-overexpressing animals *(22)* (Fig. 2A). Moreover, muscle concentrations of this metabolite correlated positively with serum levels of nonesterified fatty acids (Fig. 2B) but not circulating ketones, suggesting that its production occurs locally within the muscle as a consequence of increased lipid delivery. Further studies revealed that exposure of L6 myotubes to elevated concentrations of fatty acids not only induces enzymes of

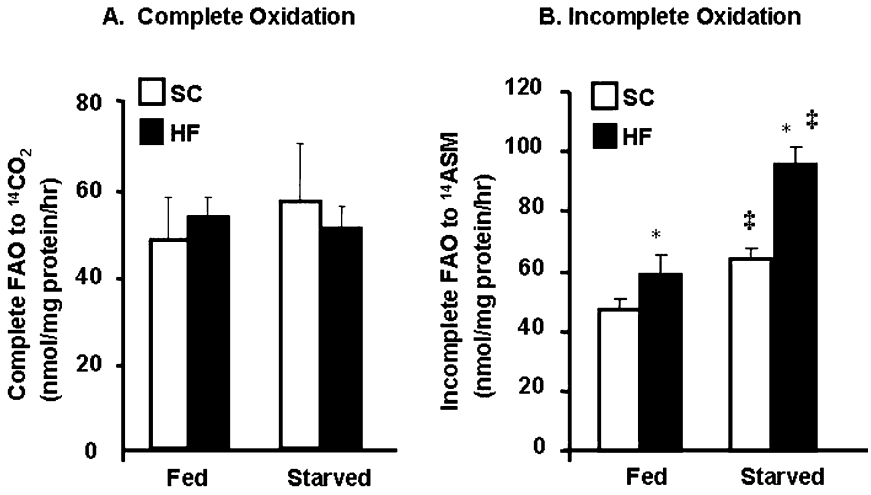



**Fig. 1.** Fatty acid oxidation in rat muscle mitochondria. Mitochondria were isolated from whole gastrocnemius muscles harvested in the ad lib fed or 24 h starved state from rats fed on a either a standard chow (SC) or high fat (HF) diet for 12 wk. Mitochondria were incubated in the presence of 150 μM [1-$^{14}$C]palmitate and radiolabel incorporation in $CO_2$ (**A**) was determined as a measure of complete oxidation, whereas label incorporation into acid soluble metabolites (ASM) (**B**) was measured to assess incomplete fatty acid oxidation. Complete and incomplete oxidation rates were normalized to total mitochondrial protein. Data are from Koves et al. *(71)*.

fatty acid oxidation, such as CPT-1, but also increases the expression of the ketogenic enzyme, mitochondrial HMG CoA synthase (Fig. 2C), while having no effect on expression of key enzymes of the TCA cycle or the electron transport chain *(22)*. Thus, this work suggests that *de novo* ketogenesis (typically thought of as a hepatic program) is induced in skeletal muscle to provide an outlet for accumulating acetyl CoA, made necessary by increased β-oxidative flux occurring without a coordinated adjustment in TCA cycle activity. The profile of other acylcarnitine species obtained by tandem MS also support the notion of incomplete β-oxidation in animal models of insulin resistance. Such profiles demonstrate that multiple fatty acylcarnitine metabolites, including long-chain acylcarnitines such as palmityl- and oleyl-carnitine, were abnormally high in obese compared to lean rats *(22,71)*. Moreover, rats fed a standard chow diet exhibited decreased levels of acylcarnitines in muscle during the transition from the fasted to the fed states, whereas in comparison, rats on the high-fat diet exhibited little or no change (Fig. 3A). Finally, a 3-wk exercise intervention in mice fed on a chronic high-fat diet lowered muscle acylcarnitine levels (Fig. 3B), in association with increased TCA cycle activity and restoration of glucose tolerance *(71)*.

These studies also highlighted important roles for PGC1α and PPAR transcription factors in mediating lipid-induced metabolic adaptations *(71)*. Similar to muscle mitochondria from high-fat fed rats, L6 myocytes exposed to increasing fatty acid concentrations exhibited disproportionate increases in the rates of incomplete (assessed by measuring incorporation of the label from [$^{14}$C] oleate into acid-soluble β-oxidative intermediates) relative to complete (label incorporation into $CO_2$) β-oxidation of fatty acids. Overexpression of PGC1α in lipid-cultured L6 cells caused production of $^{14}CO_2$ to increase and maintain pace with production of [$^{14}$C]-labeled acid-soluble β-oxidative intermediates (Fig. 4A). In other words, the ratio of complete to incomplete β-oxidation was dramatically increased by PCG1α expression (Fig. 4B). Consistent with these functional assessments, cDNA microarray analyses showed that fatty acid exposure in the context of low PGC1α activity resulted in the induction of classic PPAR-targeted genes involved in lipid trafficking, glucose sparing and β-oxidation, but with little or no change in other downstream pathways that regulate respiratory capacity. In contrast, high PGC1α expression enabled the coordinated induction of β-oxidative enzymes with equally important downstream targets (e.g., TCA cycle, ETC, and NADH shuttle systems). These findings imply that PGC1α enables tighter coupling between β-oxidation and the TCA cycle.

Taken together, these metabolic studies underscore several important points. First, the accumulation of fatty acylcarnitines in muscle of obese/insulin resistant rats implies increased rather than decreased rates of

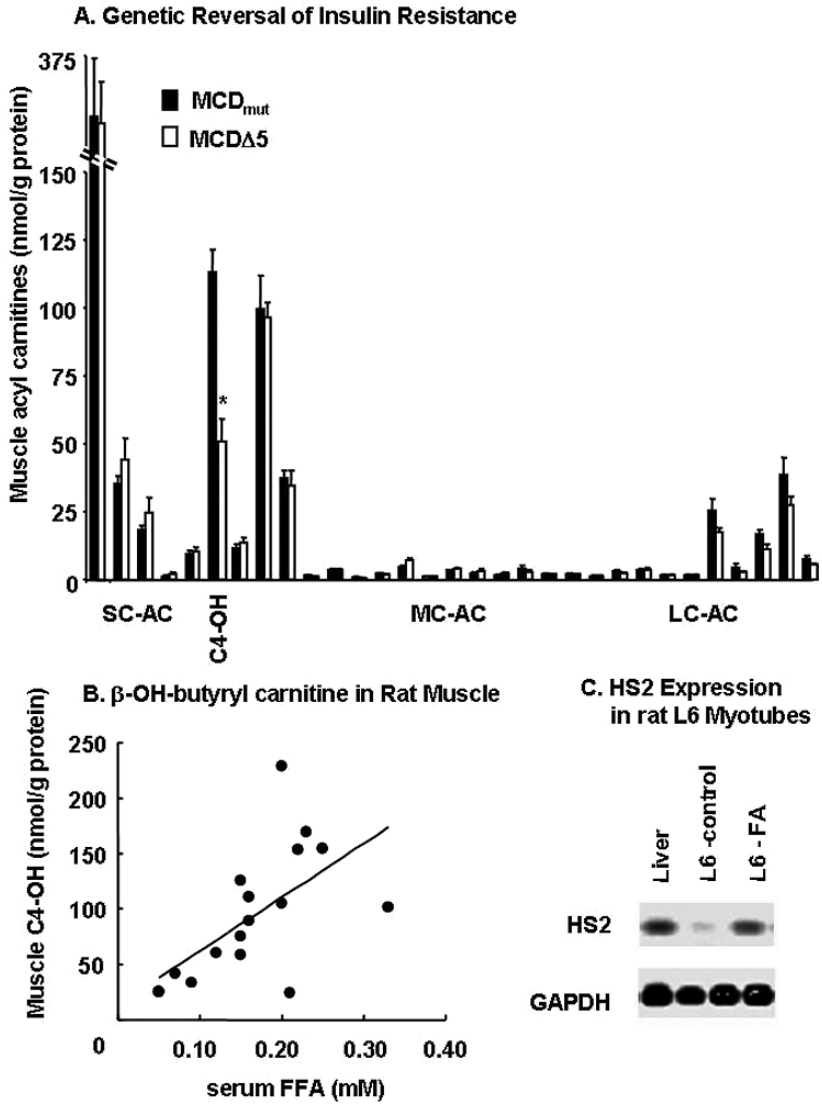



**Fig. 2.** Reversal of insulin resistance corresponds with reduced β-OH-butyryl-carnitine levels in muscle. **A**) Tandem mass spectrometry-based analysis of short (SC), medium (MC) and long (LC) chain acyl carnitine species in gastrocnemius muscles. Wistar rats were fed on a high-fat diet for 11 wk before virus treatment and muscles were harvested 5 d after injections of adenoviruses encoding active malonyl-CoA decarboxylase (AdCMV-MCD Δ5) or an inactive mutated form of the enzyme (AdCMV-$MCD_{mut}$). **B**) Linear regression analysis of β-OH-butyrate (C4-OH) levels in muscle versus serum free fatty acids (FFA). **C**) Semiquantitative RT-PCR analysis of HMG-CoA synthase 2 (HS2) mRNA, normalized to glucose-6-phosphate dehydrogenase, G6PDH mRNA, in fully differentiated rat L6 myotubes incubated without (L6-control) or with 500 μM oleate (L6-FA) for 24 h. RNA from liver of fasted rats was analyzed as a positive control. Data are from An et al. *(22)*.

**Fig. 4.** PGC1α enhances complete oxidation of fatty acids. Fatty acid oxidation was evaluated in rat L6 myocytes treated with recombinant adenoviruses encoding β-galactosidase (β-gal) or PGC1α, compared against a no virus control (NVC) group. Forty eight h after addition of virus, cells were incubated 3 h with 100-500 μM [$^{14}$C]oleate. **A**) Complete fatty acid oxidation was determined by measuring $^{14}$C-label incorporation into $CO_2$. **B**) The relationship between incomplete and complete fatty acid oxidation was expressed as a ratio of label incorporated into acid soluble metabolites (ASM) divided by labeling of $CO_2$. Differences among groups were analyzed by ANOVA and Student's *t*-test, * indicates $P < 0.05$ comparing PGC1α to NVC and β-gal treatments, ‡ indicates $P < 0.05$ comparing low and high FA conditions. Data are from Koves et al. *(71)*.

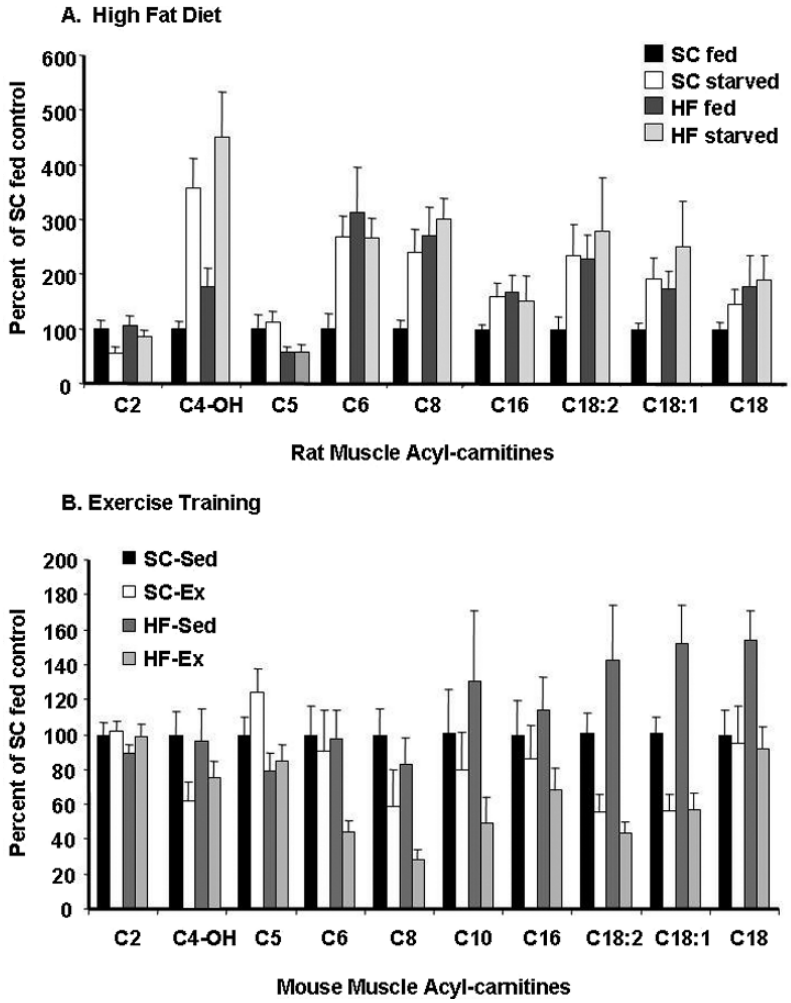
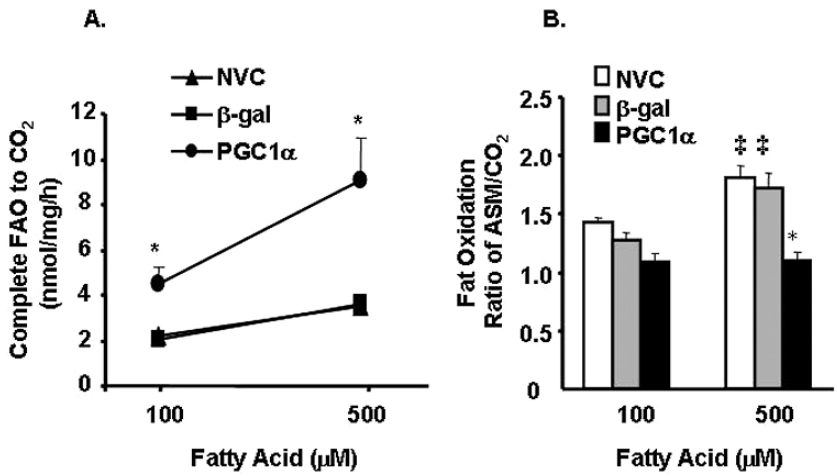



**Fig. 3.** Muscle acylcarnitine profiling in diet-induced insulin resistance and exercise training. **A)** Gastrocnemius muscles were harvested from rats fed ad libitum (fed) or starved 24 h after 12 wk on either a standard chow (SC) or high fat (HF) diet. **B)** Gastrocnemius muscles were harvested from mice fed on standard chow (SC) or high fat (HF) diets for 14 wk. During the final 2 wk of the diet half of the mice in each group were kept sedentary (Sed) or exercise trained (Ex) by running wheel. Muscle acylcarnitine profiles were evaluated by tandem mass spectometry and are expressed as a percent of SC-fed controls. Data are from Koves et al. *(71)*.



mitochondrial fatty acid uptake and β-oxidation. Second, experiments in isolated mitochondria from high-fat rats suggest that PPAR-mediated increases in β-oxidative activity exceeded the capacity of the TCA cycle to fully oxidize the incoming acetyl-CoA. This supports the idea that assessment of complete fat oxidation via measurement of $CO_2$ production provides only a partial view of lipid catabolism. Lastly, the acylcarnitine profiles from fed and fasted rats suggested that mitochondria from obese animals were unable to appropriately adjust mitochondrial fatty acid influx in response to nutritional status, thus supporting the observation of metabolic inflexibility in humans *(57)*.

The foregoing findings now provide a potential reconciliation of current prominent hypotheses of metabolic perturbations leading to muscle insulin resistance (summarized schematically in Fig. 5). The new model holds that fuel oversupply to muscle results in enhanced fatty acid β-oxidation due both to transcriptional regulation and increased substrate supply. However, in the absence of work (i.e., exercise), the TCA cycle not only remains

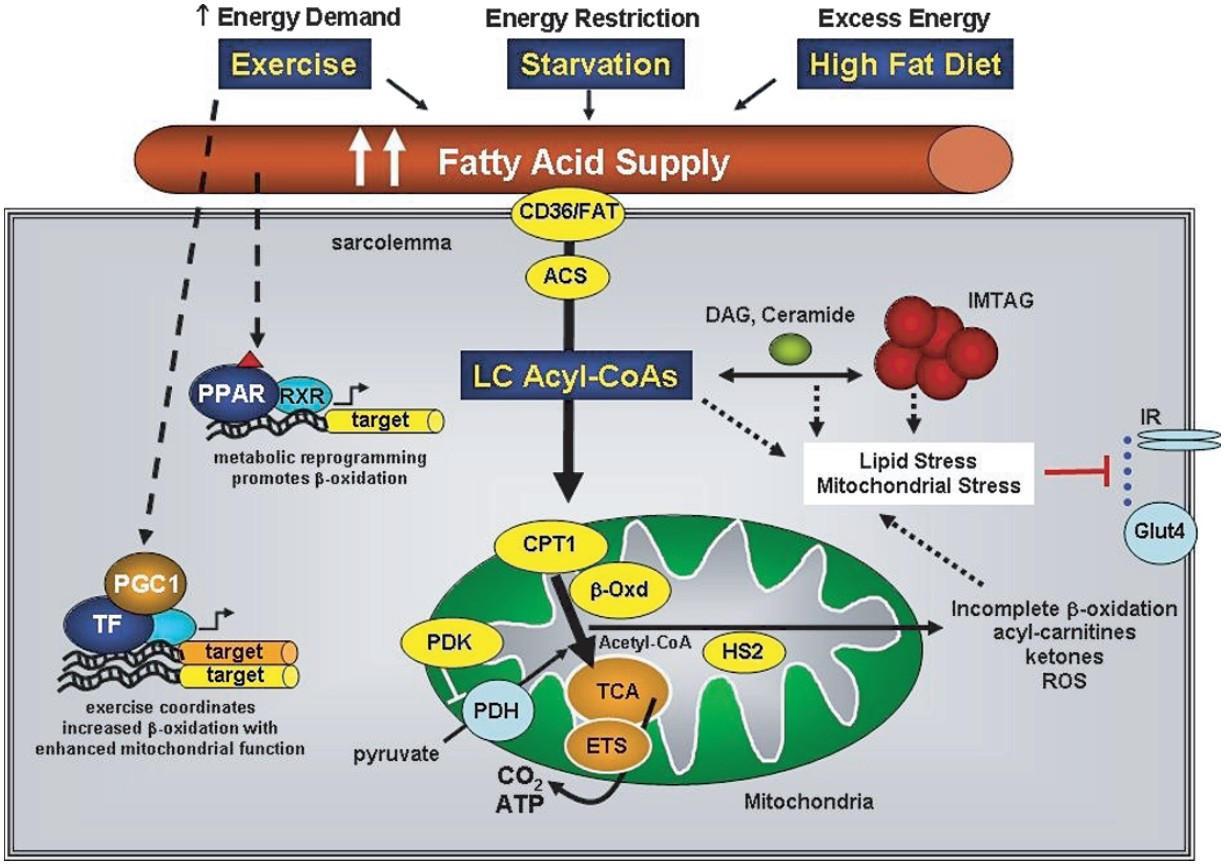



**Fig. 5.** Proposed model of lipid-induced insulin resistance in skeletal muscle. During conditions of overnutrition, starvation and/or inactivity, fatty acid influx and peroxisome proliferator-activated receptor (PPAR)-mediated activation of target genes (*in yellow*) promotes β-oxidation without an accompanying increase in tricarboxylic acid (TCA) cycle enzymes. TCA cycle flux and complete fat oxidation is further hampered by a high energy redox state (rising NADH/NAD and acetyl-CoA/free CoA ratios). As a result, metabolic by-products of incomplete fatty acid oxidation (*acylcarnitines*, *ketones and reactive oxygen species (ROS)*) accumulate, which in turn gives rise to the accumulation of LC-CoA species and subsequent production of other lipid-derived metabolites, such DAG, ceramide and IMTAG. Together, these mitochondrial and lipid-derived stresses impinge upon insulin signal transduction, thus inhibiting glucose uptake and metabolism (*in blue*). Exercise combats lipid stress by activating PPARγ coactivator 1 α (PGC1α), which coordinates increased β-oxidation with the activation of downstream metabolic pathways (*in orange*), thereby promoting enhanced mitochondrial function and complete fuel oxidation. Tighter coupling of β-oxidation and TCA cycle activity alleviates mitochondrial stress, lowers intramuscular lipids and restores insulin sensitivity. Abbreviations: ACS; acyl-CoA synthase, β-Oxd; β-oxidative enzymes, CD36/FAT; fatty acid transporter, CPT1; carnitine palmitoyltransferase 1, DAG; diacylglycerol, ETC; electron transport chain; Glut4; glucose transporter 4, HS2; mitochondrial HMG-CoA synthase, IMTG; intramuscular triacylglycerol, IR; insulin receptor, LC-CoAs; long-chain fatty acyl-CoAs; PDH; pyruvate dehydrogenase; PDK; pyruvate dehydrogenase kinase, ROS, reactive oxygen species, TF; transcription factor.

inactivated at a transcriptional level, but moreover, flux through the pathway is inhibited by the high energy redox state that prevails under circumstances of overnutrition. As a result, acetyl CoA accumulates and forces accumulation of other acyl CoA species (as reflected by acylcarnitine profiling). This leads in turn to increased production of other lipid-derived molecules, including TAG, diacylglycerol, ketones, ceramides and reactive oxygen species, as well as other yet unidentified metabolites that could contribute to or reflect mitochondrial stress.

An important question remaining is whether the high rates of fatty acid catabolism in the obese state are insufficient to compensate for increased lipid delivery, thereby allowing excess lipid-derived metabolites to impair insulin signaling, or alternatively, whether persistently high rates of mitochondrial β-oxidation directly contribute to the development of insulin resistance. These possibilities are not necessarily mutually exclusive. Assuming that insulin resistance originally evolved as a survival mechanism, it is likely that nature has devised several distinct metabolic and molecular roadways leading to the same (dys)functional endpoint. Future studies are certain to reveal new clues as to how these pathways intersect, and perhaps more importantly, how they can be circumvented by behavioral and/or pharmacological therapies.

## ACKNOWLEDGEMENTS

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# 4 Fat Metabolism in Insulin Resistance and Type 2 Diabetes

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***CONTENTS***



**Key Words:** Free fatty acid; insulin resistance; adipocyte; inflammation; fatty acid transporter.

## INTRODUCTION

The increasing prevalence of obesity and type 2 diabetes in developed and developing countries over the past few decades is in large part owing to lifestyle changes that promote excessive energy intake and reduced energy expenditure. Energy balance and metabolic homeostasis are tightly controlled by interconnected nutritional, hormonal, and neural regulatory systems, which are responsible for finely tuned responses in feeding behavior and metabolic processes. One consequence of nutrient overload and positive net energy balance is the development of resistance to the normal action of insulin. Increased free fatty acid (FFA) flux from adipose tissue to nonadipose tissues, resulting from abnormalities of fat metabolism (either storage or lipolysis), is both a consequence of insulin resistance and an aggravating factor, participating in and amplifying many of the fundamental metabolic derangements that are characteristic of insulin resistance and type 2 diabetes. Adverse metabolic consequences of increased FFA flux and cytosolic lipid accumulation include, but are not limited to, dyslipidemia, impaired hepatic and muscle metabolism, decreased insulin clearance, and impaired pancreatic β-cell function. In addition, there is increasing appreciation that obesity and insulin resistance are chronic inflammatory states, with inflammatory mediators aggravating obesity-associated insulin resistance. There is growing evidence that FFAs activate the NFκB inflammatory pathway through action on the IKKβ kinase, thereby amplifying a pro-inflammatory response, which is tightly linked to impaired insulin signalling. Weight loss through reduction of caloric intake and increase in physical activity, among other effects reduces plasma FFAs, and cytosolic triglycerides (TGs) in extra-adipose

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tissue, and can prevent the development of, and ameliorate the adverse manifestations of, diabetes. Future therapies that specifically modulate fat metabolism by inhibiting adipose tissue lipolysis or by activating fatty acid oxidation, thereby reducing plasma FFA concentrations and tissue lipid accumulation, may result in improvement in some or all of the above metabolic derangements, or prevent progression from insulin resistance to type 2 diabetes. This chapter will expand on these concepts by highlighting the mechanisms underlying dysregulation of fatty acid metabolism in insulin resistant states, the causative role of fatty acid metabolites in initiating and aggravating these metabolic disorders, and possibilities regarding fat metabolism as a therapeutic target.

## MAINTENANCE OF WHOLE-BODY GLUCOSE AND FFA HOMEOSTASIS

### *Glucose and FFA Homeostasis*

In the postabsorptive (fasting) state, energy is derived primarily from the breakdown of endogenous fat stores, whereas hepatic, and, to a lesser extent, renal endogenous glucose production maintains blood glucose levels for utilization by organs such as the brain. Fatty acids derived from lipoprotein breakdown or released as FFAs from adipose tissue are oxidized as the main source of energy (Fig. 1 and Color Plate 2, following p. 34). Postprandially there is a shift toward storage of energy metabolites, mediated to a large extent by

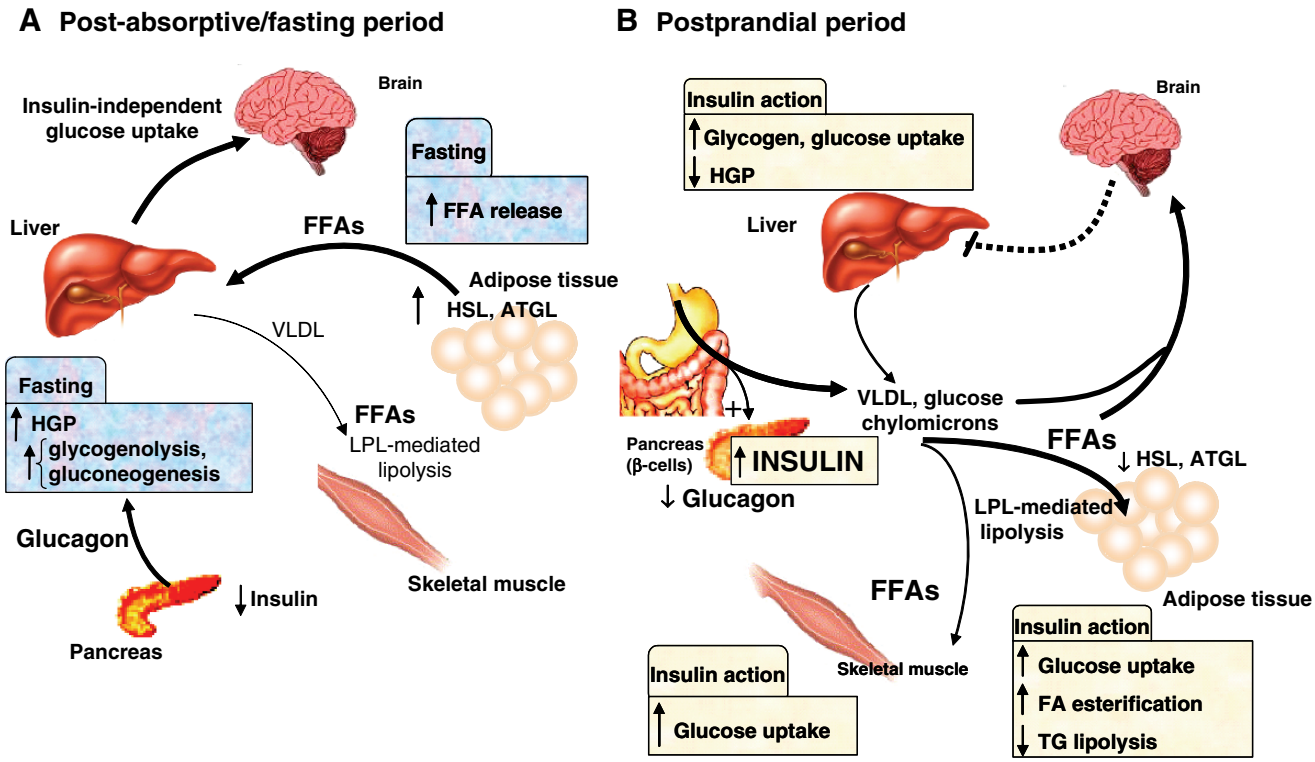


**Fig. 1.** Glucose and FFA homeostasis. **A**. Postabsorptive/fasting period: Stimulation of adipose tissue lipases, HSL and ATGL, by low plasma insulin concentrations and elevated glucagon, facilitates mobilization of stored triglycerides, releasing fatty acids into the circulation. Low insulin and high glucagon also stimulates gluconeogenesis from FFA and other gluconeogenic substrates and facilitates fatty acid transport into the mitochondria of hepatocytes, where they are utilized for β-oxidation and formation of ketone bodies. **B**. Postprandial period: Insulin is secreted by pancreatic β-cells in response to rising blood glucose, FFA and other secretatogogues. Insulin inhibits hepatic glucose production and stimulates glucose uptake, utilization and storage in insulin sensitive tissues such as muscle, liver and adipose tissue. Adipose tissue lipolysis is suppressed and lipolysis of triglyceride rich lipoproteins (chylomicrons and VLDL) by lipoprotein lipase is stimulated by insulin, with net fatty acid uptake by adipose tissue. Hepatic glucose production is suppressed and glycogen storage stimulated by direct insulin action as well as indirectly by suppression of plasma FFAs and by neuronal signals eminating from the hypothalamus, which senses nutrients directly. Abbreviations are: ATGL = adipose triglyceride lipase; FA = fatty acid; FFAs = free fatty acids; HGP = hepatic glucose production; HSL = hormone sensitive lipase; LPL = lipoprotein lipase; VLDL = very low density lipoprotein (*see* Color Plate 2, following p. 34).

nutrient-induced insulin secretion. The postprandial rise of plasma glucose, fatty acids, amino acids, and incretin hormones stimulates the release of insulin by pancreatic β-cells, which serves to stimulate glucose uptake by insulin sensitive tissues such as muscle and adipose tissue and suppresses glucose production by liver and kidney (Fig. 1 and Color Plate 2, following p. 34). In addition, insulin suppresses FFA release from adipose tissue and favors their storage as TGs. Maintenance of whole-body glucose and lipid homeostasis depends upon normal insulin secretion by pancreatic β-cell and normal tissue sensitivity to insulin *(1,2)*.

## GENERAL OVERVIEW OF THE MAJOR ORGANS INVOLVED IN GLUCOSE AND FFA HOMEOSTASIS AND ORGAN CROSS-TALK

The ability of the organism to sense energy status and switch between demand for energy substrates in the fasted state and their storage in the postprandial state involves close communication between the organs involved in energy homeostasis, and integration of endocrine (hormones, adipocytokines, inflammatory cytokines), metabolic (glucose, FFAs, amino acids and intermediary metabolites), and neural signals. Liver, pancreas, brain, muscle, intestine, and adipose tissue are the major organs involved in co-ordination of energy metabolism. These organs are able to communicate with each other and to sense the energy status of the entire organism, thereby co-ordinating their function, but the precise mechanism of this communication remains poorly understood. Two examples illustrate this point. It is still not known, for example, how the healthy pancreas "senses" small variations in extrapancreatic tissue insulin sensitivity in the absence of a rise in blood glucose, to modify insulin secretion acutely and chronically, thereby maintaining normoglycemia *(3)*. Likewise, it is not well understood how the silencing of a key regulator of glucose uptake, GLUT4, in one tissue such as skeletal muscle results in significant changes in insulin sensitivity and glucose uptake in another organ such as adipose tissue *(4)*. The converse also appears to be true, where downregulation of GLUT4 and glucose transport selectively in adipose tissue has been shown to cause insulin resistance in muscle *(5)*, perhaps by diverting FFAs and other fuels from adipose to nonadipose tissues. Plasma FFAs have long been implicated in mediating the cross talk among organs, and no doubt play an important role, but with the recent discovery of many additional modulators of insulin sensitivity and metabolic processes, it seems increasingly unlikely that a single factor is responsible for cross talk among organs. Instead, a complex array of metabolic, endocrine, and neural signals likely underlies the remarkable coordination of energy homeostasis.

The *liver* plays a pivotal and unique role in maintaining whole-body glucose and FFA homeostasis. It has the ability to either synthesize lipids via the *de novo* lipogenic pathway, or to use them for energy by mitochondrial β-oxidation, depending on the energy status of the organism. In the fasting state, glucose is produced predominantly by the liver, by gluconeogenesis and glycogen breakdown (glycogenolysis), to ensure sufficient glucose supply to the central nervous system. Postprandially, insulin suppresses hepatic glucose production (HGP) by both direct and indirect mechanisms.

Insulin secreted by the *pancreas* plays a central role in the switch from postabsorptive (fasting) to postprandial metabolic response *(6)*. Although insulin acts directly on hepatic insulin receptors to suppress hepatic glucose production *(7)*, insulin-mediated reduction of FFA release from adipose tissue participates indirectly in the inhibition of HGP *(8,9)*.

As discussed below in more detail, liver metabolism can be controlled "indirectly" by the *brain*, which plays a central integrative role as a "sensor" of the nutritional, hormonal, and neural status, integrating those stimuli to implement appropriate metabolic responses *(10)*. Thus it appears that both direct and indirect effects of insulin are involved in the inhibition of HGP, although the relative contribution of the liver, brain and extrahepatic tissues remains an open question *(7)*.

Skeletal *muscle* is responsible for a large part of total body glucose uptake (80–85% of peripheral glucose uptake) and its metabolism will be discussed in detail elsewhere in this book.

The *intestine* plays a role in organ cross-talk, not only by nutrient digestion and absorption, but also by producing signalling peptides (i.e., ghrelin, cholecystokinin.), which can alter appetite and food intake *(11)*, as well as by secreting in a nutrient-dependent manner the incretins GLP-1 and GIP, peptides which stimulate insulin secretion in response to glucose, delay gastric emptying, inhibit glucagon secretion and inhibit apetite *(12)*.

*Adipose tissue* is the largest energy storage organ in the body, storing energy in the form of triglycerides and mobilizing them by lipolysis, with release of fatty acids and glycerol into the circulation *(13)*. Recently,

however, there has been growing appreciation that adipose tissue is more than simply a fat storage and buffering compartment. It is an extremely active endocrine organ, playing an important role in signalling to muscle, liver, and central nervous system by secreting the so-called adipocytokines (leptin, resistin, adiponectin) and inflammatory mediators such as TNFα, IL-6, and PAI-1 *(14)*.

### *FFAs as Signaling Molecules*

Rossetti and collaborators have shown through an elegant set of in vivo studies in rodents that a sustained elevation of plasma FFAs induces a rise in the LCFA-acylCoA pool within the hypothalamus, which acts as a signal for nutrient availability, and which is sufficient to inhibit both food intake and hepatic glucose production *(15,16)*. Central administration of oleic acid is able to mimic the effects of plasma FFAs on feeding behavior, and pharmacological intervention aimed at reducing intracellular LCFA-acylCoA abundance, either by blunting their synthesis or by favoring their oxidation, induces a derepression of food intake. Hypothalamic fat oxidation, as well as insulin infusion, suppresses HGP, an effect abolished by vagotomy *(17)*. The role of elevated FFAs in the signal transmission has been further corroborated by experiments showing that inhibition of food intake by intraventricular administration of oleic acid is blunted by overfeeding in rats, indicating that impairment of the brain response to FFAs may have some deleterious consequences on food intake and consequently is likely to contribute to adiposity and associated insulin-resistance. AMP kinase (AMPK) is involved in the formation of malonylCoA via activation of ACC, thereby regulating the intracellular concentration of esterified LCFA. It is thought to act as a fuel sensor at the hypothalamic level, thereby inhibiting food intake *(10,18)*. A feedback loop has been proposed in which both nutrients (such as FFAs and glucose) *(17,19)*, and hormonal stimuli (such as leptin or insulin) *(20)*, converge on the brain, which in turn limits nutrient ingestion and output from endogenous stores.

Supporting their role as signalling molecules, FFAs are able to modulate the activity of transcription factors involved in lipid and carbohydrate metabolism, thereby modifying the expression and/or activity of proteins involved in substrate uptake/transport, in enzymes of the different metabolic pathways, or in insulin signalling. Fatty acids are ligands for various nuclear receptors (PPARs, LXRs, or HNF-4α) and increase expression of some transcription factors such as SREBP1c and ChREBP, which are master regulators of *de novo* lipogenesis. Downstream effects of fatty acids on gene expression include increased liver, adipose, and intestinal FA transporters, increased glucose transporters, and esterifying/trapping FA enzyme acylCoA synthase, and they can more generally modulate metabolic pathways such as FA β-oxidation, lipogenesis, or gluconeogenesis by acting on key rate-limiting steps involved therein *(21)*.

From these data, fatty acids appear to act as important signalling molecules in energy homeostasis, and altered FFA metabolism may therefore have critical and deleterious consequences for whole-body fuel utilization and/or storage. Indeed, disorders of either fat storage or mobilization (leading to elevated plasma FFAs) are central in the pathogenesis of many of the metabolic features of the insulin resistance syndrome and type 2 diabetes. We will discuss the consequences of these abnormalities for hepatic glucose production, insulin action in muscle and liver, insulin clearance, and pancreatic β-cell function, and examine strategies for reducing FFAs and their physiological consequences.

## ABNORMALITIES OF FFA METABOLISM IN OBESITY, INSULIN RESISTANCE, AND TYPE 2 DIABETES

### *Elevated Plasma FFA as Markers of Insulin Resistance, Type 2 Diabetes, and Cardiovascular Disease.*

Although studies with small numbers of subjects often fail to show a significant elevation of plasma FFA concentration in those with insulin resistance or Type 2 diabetes, fasting plasma FFAs have generally been found to be elevated when examined in large, well-characterized populations of individuals with obesity, insulin resistance, and type 2 diabetes *(22,23)*. Postprandial FFA levels may also be higher in obese, insulin resistant individuals *(24)* and in individuals with type 2 diabetes *(25,26)*. Prospective epidemiologic studies have suggested that elevated plasma FFA is an independent predictor of progression to type 2 diabetes in Caucasians and Pima Indians *(27–30)*. This was confirmed in a large cohort of African-American and Caucasian men and women

*(23)*. Although some studies did not find an elevation of fasting plasma FFA in first-degree relatives of patients with type 2 diabetes *(31–33)*, other studies have shown that elevated fasting plasma FFA correlated with low insulin-mediated glucose disposal in these individuals *(34–36)*. Elevated FFAs have also been associated with an increased risk of myocardial ischemia *(37)*, and they induce impaired large artery endothelial *(38)* as well as microvascular function *(39)*. FFAs have also been correlated to carotid intima-media thickness *(40)*.

### *What is the Pathophysiology of Elevated Plasma FFAs?*

Plasma FFA concentration reflects a balance between release (by the intravascular lipolysis of triglyceride-rich lipoproteins and lipolysis of predominantly adipose tissue triglyceride stores) and tissue uptake (predominantly re-esterified in adipose tissue and liver and oxidized in muscle, heart, and liver). In the postabsorptive state, the systemic FFA concentration is determined largely by the rate of FFA entry into the circulation, but postprandially the rate of uptake/esterification, particularly by adipose tissue, is also a critical determinant of plasma FFA concentration (Fig. 2 and Color Plate 3, following p. 34).

#### Enhanced Adipose Tissue Lipolysis (Fig. 2 and Color Plate 3, following p. 34)

Lipolysis (hydrolysis) of adipose tissue TG stores mobilizes energy by releasing FFAs and glycerol into the circulation, to be utilized by other tissues. The lipolytic process, as assessed by circulating levels of FFAs and glycerol, displays diurnal variability *(41,42)*. Until very recently, the hydrolysis of TG within the adipocyte was

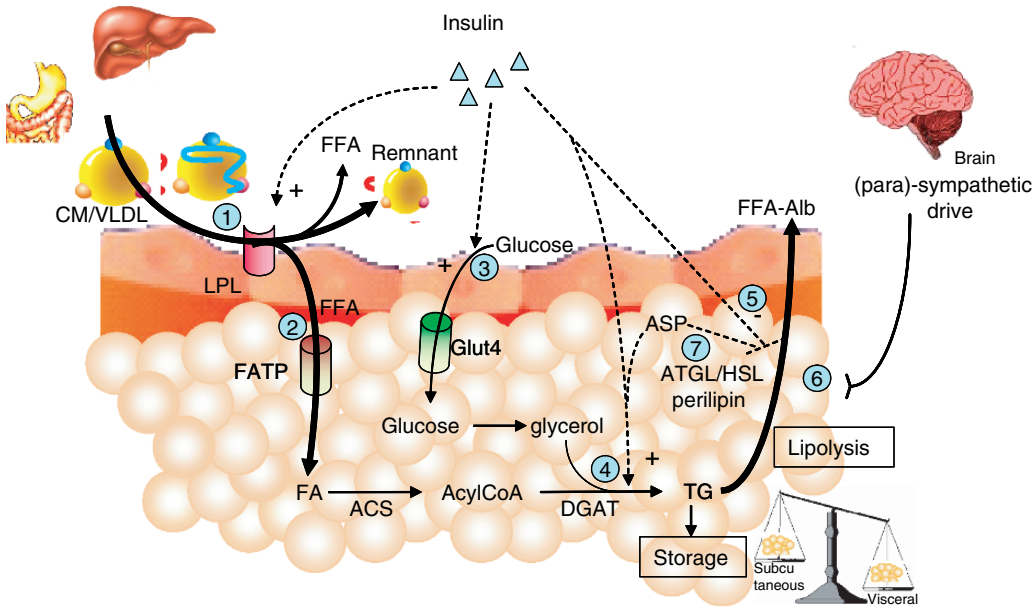


**Fig. 2.** Control of fatty acid uptake and release by adipose tissue**.** Insulin promotes FFA uptake into the adipocyte by stimulating the LPL-mediated release of FFA from lipoprotein triglyceride (1). Fatty acids enter the adipocyte both by diffusion down a concentration gradient as well as by facilitated transport by fatty acid transporters (2). Insulin also stimulates glucose transport into the adipocyte, thereby increasing the availability of glycerol-3P for triglyceride synthesis (3). Insulin may have a direct stimulatory effect on lipogenic enzymes such as DGAT (4). By inhibiting HSL and ATGL (5), it reduces the intracellular lipolysis of cytosolic triglycerides, thereby promoting adipocyte triglyceride storage. Parasympathetic output from the brain may inhibit lipolysis directly (6). ASP (7), whose action is complementary to that of insulin in the adipocyte, stimulates glucose uptake and fatty acid esterification and inhibits mobilization of stored triglycerides. Defective adipose tissue trapping and esterification or enhanced lipolysis of stored triglycerides as occurs in insulin resistance would result in elevated FFA flux from adipose to non-adipose tissue.
Abbreviations are: ACS, acylCoA synthase, ASP = acylation stimulating protein, FFA-Alb = albumin bounded fatty acid, CM = chylomicron, DGAT = diacylglycerol acyltransferase, FFA = free (nonesterified) fatty acid, FA = fatty acid, FATP = fatty acid transport protein, GLUT = glucose transporter, Glycerol-3P = glycerol-3 phosphate, DAG = diacylglycerol, HSL = hormone sensitive lipase, LPL = lipoprotein lipase, TG = triglyceride, VLDL = very low density lipoprotein. Solid lines indicate flux of metabolic substrates and dashed lines indiated stimulatory or inhibitory effects of insulin. '+' indicates a stimulatory effect of insulin and "–" indicates an inhibitory effect of insulin (*see* Color Plate 3, following p. 34).

thought to be catalyzed mainly by hormone sensitive lipase (HSL). Hormones with lipolytic activity such as glucagon and catecholamines activate HSL by phosphorylation via cAMP-mediated activation of PKA, whereas the major antilipolytic hormone, insulin, exerts a strong suppressive effect on HSL activation. HSL-mediated lipolysis requires caveolin-1-facilitated PKA phosphorylation of a protein named perilipin A, present at the surface of lipid storage droplets. Perilipin A phosphorylation allows HSL to gain access to the surface of lipid droplets, to participate in lipolysis of stored triglycerides *(43,44)*. A number of studies have shown a diminished suppressive effect of insulin on the rate of appearance of FFA in obese and nonobese insulin resistant humans *(45,46)*. Resistance to insulin's suppressive effect on HSL also appears to be present postprandially in insulin resistance and type 2 diabetes *(47)*. Although the diminished whole body insulin suppressive effect on FFA rate of appearance seen in insulin resistant individuals has readily been assumed to be owing to resistance to insulin suppression of HSL, HSL is normally exquisitely sensitive to the suppressive effects of insulin, and it is not clear how important this mechanism is in individuals whose peripheral tissue insulin concentrations are generally elevated. The mass effect of FFA released from expanded body fat depots may also play an important role. A number of in vitro studies have in fact failed to demonstrate either increased HSL activity and basal lipolytic rate in adipose tissue from obese individuals or resistance to insulin's suppressive effect on HSL *(48)*.

An important clue to the existence of other adipose tissue lipase enzymes came from studies of mice lacking HSL, because they have normal body weight and reduced, not increased, fat mass *(49–51)*, and exhibit accumulation of diacylglycerol (DAG) in fat cells *(52)*. In addition, HSL-deficient mice showed that HSL-independent lipolysis is increased upon fasting *(53)*. These data suggested that at least one other unidentified lipase exists, which is presumably responsible for the hydrolysis of TG into DAG, the latter being the main substrate for HSL. Indeed, Zechner and collaborators recently discovered a new lipase that is highly expressed in adipose tissue, which they named "adipose triglyceride lipase" (ATGL) *(54)*. ATGL initiates the hydrolysis of TG, generating DAGs and FAs. Lipases identified at more or less the same time by Villena et al., and Jenkins et al., called desnutrin and the calcium-dependent phospholipase iPLA2ζ respectively, were later found to be identical to ATGL *(36,55)*. ATGL associates with lipid droplets, and is under the control of hormonal regulation by glucocorticoids (upregulation) and insulin (downregulation), and its expression is reduced in a mouse model of obesity. It is likely that ATGL is responsible for lipolysis in HSL-deficient mice, although other lipases may contribute to the process. Indeed, a recent report shows that overexpression of ATGL in vitro in the 3T3-L1 cell increases basal and isoproterenol-stimulated release of FFAs and glycerol, whereas siRNA-mediated knock down of ATGL resulted in the opposite effect *(56)*. Consistent with its suppression by insulin, ATGL expression was increased in adipose tissue from diabetic insulinopenic streptozotocin-treated mice or in adipose-specific insulin receptor-deficient mice *(56)*. ATGL and HSL therefore appear to function in a co-ordinated fashion to mobilize stored adipose tissue triglycerides, with ATGL acting mainly as a triglyceride lipase, whereas HSL acts primarily at the next step, that of diglyceride lipolysis. Exactly how these two key adipose tissue lipolytic enzymes co-ordinate their actions and their differential regulation by hormones and other factors has not yet been established.

## Pulsatility of FFA Release

Oscillations in lipolysis have been described in omental tissue of dogs *(57)*. Electrical stimulation of the sympathetic nerve endings stimulates lipolysis and FFA release from adipose tissue, whereas denervation reduces lipolysis. Studies in dogs *(57)*, and more recently in humans *(58)*, confirmed that the pulsatility of FFA release is linked to neuronal activity, as β3-receptor blockade partly abrogated FFA and glycerol oscillations. Recently Karpe and colleagues confirmed pulsatility of FFA and glycerol release from subcutaneous depots in humans during euglycemic hyperinsulinemic clamps, thus demonstrating that the oscillations in fatty acid release are not dependent on insulin *(59)*. Oscillations of plasma norepinephrine as an index of sympathetic nervous system activity were not well correlated with fluctuations in FFAs release *(59)*.

The parasympathetic nervous system also participates in the release of FFAs, as demonstrated by Kreier et al., who showed that denervation of the peritoneal fat leads to decreased insulin-stimulated uptake of FFAs and glucose *(60)*, and enhanced HSL activity. Finally, it has been suggested that oscillations are conserved in isolated adipocytes, suggesting cell-autonomous oscillations of FFA release *(46)*. Glucose metabolism may participate in lipolytic oscillations *ex vivo* in rat adipocytes by generating fluctuations in LCFA-acylCoA, and oscillations

are abolished in cases of glucose depletion *(46,61)*. Additional studies are required to elucidate the mechanism involved in these oscillations and to determine their physiological significance.

## Total Fat Mass and Regional Fat Depots: What are the Differences between these Fat Depots?

Because FFAs are released into the circulation by lipolysis of adipose tissue triglycerides in relation to the size of the fat depot, the greater overall fat mass of adipose tissue in obese individuals will result in an elevation of fatty acid flux to nonadipose tissues, even in the absence of a qualitative abnormality in adipose tissue metabolism *(62)*. It is worth noting that not all fat depots make an identical contribution to the plasma pool of FFAs. Upper body fat (ie fat in the visceral and subcutaneous abdominal region), but not lower body fat is strongly associated with insulin resistance and increased risk of cardiovascular events *(63–67)* although the causal nature of this relationship and the relative importance of visceral versus subcutaneous abdominal fat *(68,69)* are still debated *(70,71)*.

There are differences in lipolysis between visceral and subcutaneous fat, with visceral fat shown to have higher lipolytic activity and lower sensitivity to the antilipolytic action of insulin *(71)*. Quantification of FFA fluxes using labeled FFA has suggested that postprandial FFA is derived mostly from nonsplanchnic areas, with only a small quantity from visceral adipose tissue, suggesting increased visceral adipose tissue as a marker rather than a cause of increased insulin resistance *(72)*. On the other hand, FFAs released by visceral fat depots are delivered directly to the liver via the portal vein, resulting in greater FFA flux to the liver in viscerally obese individuals than in those with predominantly subcutaneous obesity, perhaps contributing to hepatic insulin resistance and enhanced gluconeogenesis. Along these lines, increased FFA elevation in dogs via portal venous delivery of an intravenous synthetic lipid emulsion and heparin impairs insulin action and clearance to a greater extent than systemic delivery *(73)*.

Bergman and co-workers have recently shown that expression of genes involved in lipid accumulation and lipolysis (PPARγ, SREBP-1, HSL and LPL) were increased in visceral compared to subcutaneous fat in insulin-resistant fat-fed rats, suggesting an increased metabolic turnover of fatty acids in visceral fat *(74)*. This effect may induce lipid delivery to, and deposition of fat in, the liver, because lipogenic as well as gluconeogenic programs were induced *(74)*. In humans, a correlation was demonstrated between visceral adipose mass and hepatic FFA delivery *(75)*. However, the same study also indicated that the contribution of viscerally released FFAs to the total liver delivery represented only 5–20% *(75)*. The pathophysiological relevance of this small additional FFA supply from expanded visceral fat stores remains to be elucidated. Moreover, the contribution of subcutaneous adipose tissue has been poorly characterized, and further studies are required to resolve this issue. Of note however, total splanchnic blood supply increases postprandially *(76)* because of increased insulin and sympathetic activation after meals, as might the proportion of lipolysis from spanchnic versus subcutaneous fat. Thus, the contribution of visceral fat to hepatic FFA uptake and systemic FFA appearance could be more substantial in the postprandial than in the fasting state.

Fukuhara and coworkers have identified a new adipocytokine *(77)*, which they named visfatin, previously identified as a growth factor for B-cells (or PBEF) *(78)*. Visfatin is highly expressed in visceral fat compared to subcutaneous fat depots, and its expression increases during adipocyte differentiation and in obesity *(77)*. These investigators further demonstrated that injection of recombinant visfatin or chronic adenoviral-mediated overexpression of this protein lowers plasma glucose and insulin levels in control and streptozotocin-induced or genetically induced (KKAy mice) models of diabetes. Moreover this protein is able to bind to the insulin receptor and mimic insulin action *(77)*. Additional interest in visfatin has come from human studies showing that plasma visfatin levels are increased in type 2 diabetes *(79)*. In addition, administration of the lipid lowering PPARα activator fenofibrate, or the insulin sensitizer PPARγ ligand rosiglitazone, increased visfatin expression levels in OLETF rats *(80)*. Some caution is advised, however, because no association was found between plasma visfatin levels in humans and parameters of insulin sensitivity or visceral fat mass calculated from computer-assisted tomography *(81)*. The physiological role of visfatin still needs to be established, and further studies are necessary to determine whether it is indeed a marker of visceral fat accumulation or plays a causative role in the metabolic manifestations of insulin resistance or type 2 diabetes.

## Impaired Adipose Tissue Trapping/Uptake of Fatty Acids (Fig. 2)

Uptake and sequestration of FFAs in adipose tissue, although promoting expansion of fat mass, can be viewed in a sense as a protective mechanism to prevent exposure of other tissues to excessive FFAs and their deleterious effects in situations of positive net energy balance *(82)*. Lipoprotein lipase (LPL), anchored to the endothelial surface of capillaries in tissues such as skeletal muscle and fat, hydrolyzes TGs in the core of intestinally derived chylomicrons and hepatically derived VLDL particles. This process releases FFAs and glycerol into the local microcirculation, which must be rapidly and efficiently taken up and disposed of to prevent spillover of FFAs to nonadipose tissue with consequent lipotoxicity. In the fasting state, LPL activity is low in adipose tissue and higher in muscle, to respond to muscle energy requirements. Reciprocal changes occur in the fed state, contributing to the highly regulated partitioning of FFAs among tissues. Insulin has been shown to stimulate adipose tissue LPL activity and to reduce LPL activity in muscle, implying a preferential postprandial partitioning of lipoprotein-derived fatty acids towards adipose tissue and away from muscle *(83)*. After a meal, trapping of LPL-derived FFAs in subcutaneous fat increases from near zero to near maximal uptake within 1h, whereas FFA released by muscle LPL are taken up continuously *(84)*. Although adipose tissue of lean individuals can efficiently switch from a negative to a positive FFA balance during the transition from fasting to the postprandial state, the adipose tissue FFA balance remains negative postprandially in insulin-resistant obese individuals, despite the presence of hyperinsulinemia *(85)*. Lean, glucose tolerant relatives of patients with type 2 diabetes have an increase in postprandial glucose and triglyceride excursion, and less suppression of plasma FFA, following a mixed meal, compared with matched control subjects without a family history of diabetes *(32)*. In obesity and type 2 diabetes, insulin activation of LPL in adipose tissue is delayed and LPL activity in skeletal muscle is increased instead of decreased by hyperinsulinemia *(70,86)*. The importance of LPL in tissue FFA uptake has recently been demonstrated by experiments in which either muscle-specific or liver-specific overexpression in mice induces marked tissue lipid accumulation in either muscle or liver, respectively, with consequent insulin resistance developing in the affected organ *(87)*. Although LPL may be viewed as a first step leading to the uptake of FFA by adipose tissue, it is clear that the deposition of FFA is also regulated downstream of LPL *(88)*. Endothelial lipase (EL), a more recently discovered lipase with sequence homology to LPL and predominant phospholipase A2 activity, may also participate in FFA uptake, as demonstrated in LPL-deficient mice *(89)*.

Once taken up by the cell, FFAs are esterified, a process which is dependent on the supply of glycerol-3-phosphate derived from insulin-mediated glucose uptake by the adipocyte, which is diminished in insulin resistance *(90)*. Impaired disposal of fatty acids taken up by adipocytes will have the effect of inhibiting further uptake of fatty acids along the concentration gradient among plasma, extracellular, and intracellular fluid *(91)*. Less is known about insulin stimulatory effects on esterification enzymes than is known about its effects on LPL, but insulin may directly stimulate the enzyme that catalyzes the final step in triglyceride synthesis, acyl coenzyme A:diacylglycerol acyltransferase (DGAT) *(92,93)*. Riemens et al. have suggested that the main abnormality of fatty acid trapping is an elevated rate of escape of FFAs from esterification in adipose tissue *(91)*.

The question as to whether the transport of FFA into cells occurs through a passive diffusion process or by a facilitated mechanism involving fatty acid transport protein (FATP) remains controversial. Both processes are probably involved, although their relative importance may vary as a function of free albumin-bound FFAs versus lipoprotein-packaged TG availability *(94,95)*. In the adipocyte, aP2 may interact with HSL to facilitate FFA binding *(96)*. The "scavenger" receptor CD36/FAT is a fatty acid receptor/transporter, with particular abundance in adipose tissue, heart, and skeletal muscle, but with low expression in kidney and liver *(97)*. A deficiency of CD36 has been associated with functionally significant impairment of intracellular FFA transport *(98,99)*. Furthermore, transgenic expression of CD36 in hypertensive SHR rats ameliorates insulin resistance and lowers serum FFAs *(100)*, perhaps by improving FFA uptake in adipose tissue. Muscle-specific CD36 overexpression in mice reduces body fat and lowers serum FFAs and VLDL triglycerides, but results in elevated plasma glucose and insulin, suggesting that these mice are insulin resistant *(101)*. One may speculate that the increased FFA uptake and oxidation in muscle tissues of these animals impairs muscle glucose utilization, thereby inducing insulin resistance in a fashion analogous to that seen in mice with muscle-specific LPL overexpression *(87)*. Amelioration of insulin resistance has been seen after muscle CD36 overexpression in diabetic mice *(102)*. In contrast, the uptake of fatty acids by heart, skeletal muscle, and adipose tissues from CD36 null mice is markedly reduced (by 50–80%), whereas that of glucose is increased several fold *(103)*. CD36 deficiency is present in 2–3% of the

Japanese population, and recent evidence suggests that it may be associated with insulin resistance, dyslipidemia *(104)*, and reduction in myocardial uptake of FFA tracers in vivo *(105)*.

Fatty acid trapping is also regulated by acylation stimulating protein (ASP), a proteolytic cleavage product of the third component of complement (C3). ASP production is upregulated by insulin and by chylomicrons *(106)*. Fasting ASP correlates with postprandial TG clearance *(107)*. Postprandially, ASP is produced by adipose tissue, where it stimulates adipocyte fatty acid esterification by increasing the activity of diacylglycerol acyltransferase through a protein kinase C (PKC)-dependent pathway *(108)*. There is controversy in the literature regarding the physiological importance of ASP in controlling postprandial lipoprotein metabolism, because some *(109)* but not others *(110)* have described abnormalities of postprandial lipoprotein metabolism in ASP null mice. ASP exerts additional activities, as it increases glucose uptake in human adipocytes, decreases FFA release from those cells, and has a lipogenic effect *(1)*.

### *Fat Diversion from Adipose to Nonadipose Tissue and Lipotoxicity*

"Ectopic fat deposition" appears when the normal buffering capacity of adipose tissue is impaired or exceeded, especially during postprandial periods, and is characterized by diversion of FFAs from adipose depots and lipid deposition in nonadipose tissue (liver, muscle, heart, and pancreatic β-cells). It may occur by the following mechanisms: 1) increased tissue uptake of chronically elevated FFAs, 2) increased lipogenesis within the tissue or 3) reduced FFA oxidation. Lipid accumulation in liver and muscle is associated with insulin resistance in type 2 diabetic patients *(111)*, and magnetic resonance spectroscopy measurement of intramyocellular triglyceride (IMCT) has been associated with muscle insulin resistance in humans *(112–115)*. IMCT is also elevated in lean, glucose tolerant offspring of two parents with type 2 diabetes compared with individuals without a family history of diabetes, and it is associated with lower glucose disposal *(35)*. However, whether muscle TG accumulation is simply a marker or plays a causative role in the insulin resistance is unclear. The majority opinion at the present time is that IMCT does not itself cause insulin resistance but rather is a marker of some other abnormality that is causally linked to insulin resistance. Accumulation of lipid in the liver (ie non alcoholic hepatosteatosis) is also a feature of insulin resistance *(116)*.

Lipoatrophy, a genetic or acquired reduction or total absence of adipose tissue, in humans and animal models results in accumulation of cytosolic triglycerides to a massive extent in nonadipose tissues, and in extreme insulin resistance *(117–120)*. In A-ZIP/F-1 fatless mice, intramuscular and intrahepatic lipids were significantly reduced and insulin resistance alleviated by surgical re-implantation of adipose tissue *(118,119)*. Shulman has proposed that insulin resistance develops because of an imbalance of fat distribution among tissues *(121)*.

A key issue is whether TGs accumulate in muscle tissue of insulin resistant individuals as a result of a primary defect in fatty acid oxidation, increased total FFA flux to muscle, or owing to an imbalance between FFA uptake, esterification, TG lipolysis, and fatty acid oxidation. Kelley has described inflexibility of insulin resistant skeletal muscle in switching between lipid and carbohydrate oxidation *(122)*, whereas others have implicated inherited and acquired mitochondrial dysfunction in the accumulation of myocellular triglycerides and insulin resistance *(123,124)*.

There appears to be a reciprocal channelling of fuels between muscle and fat when one or the other tissue becomes preferentially insulin resistant. Mice with targeted disruption of GLUT4 in muscle and consequent muscle insulin resistance have a redistribution of substrate from muscle to adipose tissue *(4)*. The converse also appears to be true, where downregulation of GLUT4 and glucose transport selectively in adipose tissue has recently been shown to cause insulin resistance in muscle *(5)*, perhaps by diverting FFAs and other fuels from adipose to nonadipose tissues. This concept of adipose tissue acting as a sink to protect other tissues from the toxic effects of excessive exposure to energy substrates is further supported by the finding that overexpression of GLUT4 in adipose tissue in mice is associated with an increase in adipose tissue mass and improved whole body insulin sensitivity *(125,126)*. Strikingly, adipose-specific overexpression of GLUT4 in muscle-specific GLUT-4-deficient mice reversed insulin resistance *(127)*, and loss of GLUT-4 in both adipose tissue and muscle not only resulted in altered peripheral glucose uptake and insulin resistance, but also in redirected FFA flux through increased hepatic lipogenesis and VLDL production/secretion *(128)*. Clinically, it remains a puzzle as to why some massively obese individuals have surprisingly few manifestations of the insulin resistance syndrome *(129,130)*. One hypothesis

is that the more efficient adipose tissue fat storing capacity in these individuals could confer relative protection against lipotoxicity in nonadipose tissues.

In insulin resistant states and type 2 diabetes, enhanced rates of *de novo* lipogenesis also contribute to lipid deposition in organs such as the liver and, to a lesser extent, in other tissues. In liver and muscle, hyperinsulinemia and/or FFAs *per se* may chronically induce the expression of the sterol regulatory element-binding protein 1c (SREBP1c) *(131)*, a transcription factor that plays a key regulatory role in *de novo* lipogenesis. Furthermore, FAs activate other transcription factors of the nuclear receptor family, such as the PPARs and LXRs, which are also involved in the regulation of lipid oxidation and synthesis, respectively *(132)*. Interestingly, activation of LXR has been proposed as an antidiabetic treatment, because pharmacological activation of this nuclear receptor leads to improved peripheral insulin sensitivity and peripheral glucose disposal, although it induces severe hepatic steatosis owing to LXR-triggered *de novo* TG synthesis *(133)*.

It is noteworthy that adipose tissue-derived hormones may modulate hepatic TG content: leptin overexpression decreases hepatic lipid content in lipodystrophic A-ZIP/F-1 mice *(134)*, as does adiponectin in liver and muscle of obese mice *(135)*, both being accompanied by improved insulin sensitivity. Recently the adipocyte-derived hormone adiponectin has been shown to reverse insulin resistance associated with both lipoatrophy and obesity *(135)*. Adiponectin reduced the triglyceride content of muscle and liver in obese mice by increasing the expression of fatty acid oxidation and energy dissipation in muscle. Unger has argued against the conventional view that the physiological role of leptin is to prevent obesity during overnutrition and proposed that the role of hyperleptinemia in conditions of caloric excess is to protect nonadipocytes from steatosis and lipotoxicity by preventing upregulation of lipogenesis and by increasing fatty acid oxidation *(136–138)*. Adenoviral-mediated expression of the leptin receptor prevents lipid deposition in pancreatic β-cells *(139)*. In humans, hyperleptinemia characterizes obesity, insulin resistant states, and type 2 diabetes, suggesting that leptin resistance, not leptin deficiency, may be involved in the pathophysiology *(140)*. Elevated plasma FFA could lead to relative suppression of leptin release by adipose tissue, contributing to impaired leptin signaling in insulin resistant states *(141)*. Therefore, hyperleptinemia/leptin resistance may also to a certain extent be a consequence of abnormal FFA partitioning. A more complete discussion of adipose-derived hormones and inflammatory mediators will be presented elsewhere in this book.

In summary, adipose tissue storage and release of fatty acids, and particularly the control of these processes by insulin, is grossly abnormal in insulin resistant states. In the postabsorptive period, basal adipose tissue lipolysis is elevated, and suppression by insulin is diminished. In the postprandial period there is likely to be some diversion of fat away from adipose tissue depots and towards nonadipose tissues owing to less efficient fatty acid uptake and storage by insulin resistant adipocytes. FFA efflux from an enlarged and lipolytically active visceral fat depot may not contribute quantitatively to the majority of circulating FFAs, but because of its anatomical location and intrinsic properties appears to play an extremely important role in the manifestations of insulin resistance and type 2 diabetes. A high capacity for efficient triglyceride accumulation in adipose as well as nonadipose tissue may have presented a survival advantage in the past, during times of starvation, thus accounting for selection of a "thrifty genotype" as originally proposed by Neel in 1962 *(142)*. With current high calorie, high fat diets and sedentary lifestyle, such a thrifty genotype would accumulate excess tissue triglyceride stores, with adverse metabolic consequences. In the presence of positive net energy balance, there is ongoing accumulation of lipids in both adipose and nonadipose tissues. Cytosolic lipid accumulation in nonadipose tissues such as muscle and liver is linked to the development of insulin resistance, as these tissues also attempt to protect themselves from energy overload.

## CONSEQUENCES OF ALTERED FREE FATTY ACID METABOLISM ON MUSCLE, LIVER, AND PANCREAS

FFAs constitute an important source of energy for a variety of cells throughout the body, released from the adipose tissue when demand for fuel rises *(143)*. They enhance basal and insulin-stimulated insulin secretion, and are essential for nutrient-induced insulin secretion by β-cells *(26,144)*. However, chronically elevated FFAs may contribute to peripheral and hepatic insulin resistance *(121,145)*, as well as to β-cell dysfunction in type 2 diabetes *(146)* (Fig. 3 and Color Plate 4, following p. 34).

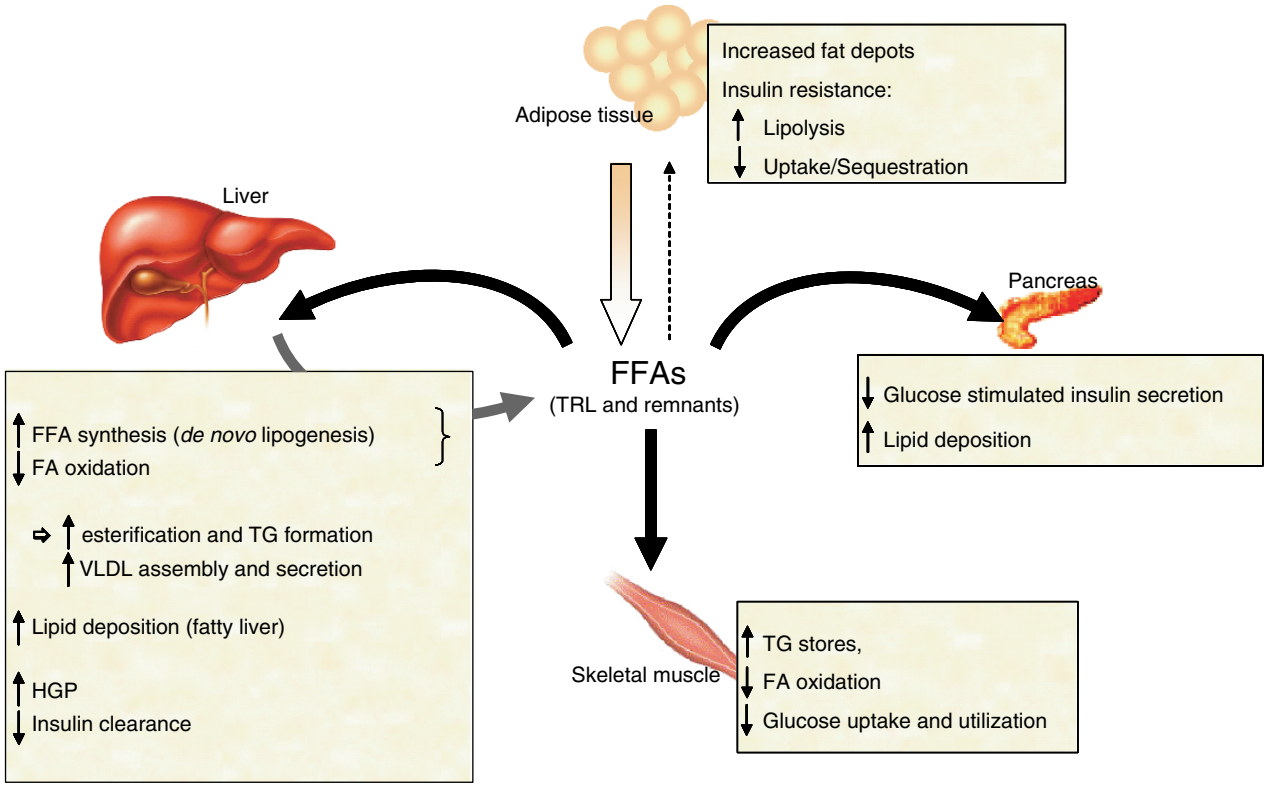


**Fig. 3.** Detrimental effects of chronic positive net energy balance. Overloading of adipose tissue beyond its storage capacity (energy intake exceeding energy expenditure) leads to lipid deposition in other tissues (skeletal muscle, pancreas, liver) via increased FFA flux and impaired FA oxidation. In turn, FFAs lead to altered insulin response/signaling, as illustrated for each of the major organs involved in energy homeostasis. Abbreviations are: FFA = free (nonesterified) fatty acid, FA = fatty acid, HGP = hepatic glucose production, LPL = lipoprotein lipase, TG = triglyceride, VLDL = very low density lipoprotein, TRL = triglyceride-rich lipoprotein (*see* Color Plate 4, following p. 34).

### *Effects of FFA on Muscle Glucose Metabolism*

Individuals with type 2 diabetes have reduced insulin-stimulated muscle glucose uptake compared to controls *(147)*. It is now well established that elevated FFAs impair glucose metabolism in muscle, and multiple mechanisms appear to be responsible, including impaired cellular glucose uptake and oxidation. A detailed discussion of muscle metabolism is presented elsewhere in this book.

### *Effects of FFA on Hepatic Glucose Metabolism*

Endogenous glucose production and hepatic insulin resistance are increased in type 2 diabetes *(32,129,148)*. Elevation of FFAs has been linked to increased HGP in dogs *(149)* and have been shown to stimulate gluconeogenesis *(145,150)*. This has been attributed to an increased intracellular pool of acetylCoA, derived from FFA β-oxidation, which can activate pyruvate carboxylase and increase NADH and ATP, which serve as co-factor and source of energy, respectively, for the gluconeogenic pathway. In addition, FFA elevation induced experimentally by infusion of Intralipid (an exogenous source of TG) and heparin (to stimulate LPL, which hydrolyzes intralipid TGs, thereby raising plasma FFAs) has been shown to increase levels of citrate formed from FA oxidation, thereby inhibiting phosphofructokinase1 and stimulating glucose production *(151)*. Two additional pathways have been proposed to explain FFA-mediated induction of gluconeogenesis: the glyoxalate and pentose-5-phosphate pathways *(152)*. In some cases, however, the net effect of FFAs on HGP is not clear, owing to a compensatory decrease in glycogen breakdown and release as glucose *(153–156)*. This counterregulation has been referred to as "hepatic auto-regulation". Both intra- and extrahepatic mechanisms contribute to this phenomenon. Intrahepatic mechanisms include activation of glycogen synthase, whereas the phosphorylase is inhibited by increased intra-

cellular levels of glucose-6-phosphate from gluconeogenesis *(154,157)*. The extrahepatic explanation relies on the ability of elevated FFAs to induce secretion of insulin and changes in portal levels of insulin. The effect of FFAs on HGP has been questioned, because in conditions where insulin levels are clamped, HGP is not increased *(158–161)*, and the auto-regulatory compensation is abolished, presumably because, at hyperinsulinemic levels, glycogenolysis is already fully suppressed *(9,162–164)*. Indeed, it has been demonstrated that when endogenous insulin secretion is blocked by use of somatostatin, and an insulin infusion allows for maintenance of basal insulin level, HGP is induced *(165)*, although opposite findings have also been reported *(154)*.

Feeding a high fat diet has been shown to increase basal HGP in overnight fasted rats *(166)*. In addition, in the same model, prolonged elevation of FFAs increased HGP despite elevation of insulin secretion and higher insulin levels *(151)*. From these observations it appears that the auto-regulation is not effective when glycogen stores are depleted. It may be hypothesized that elevated FFAs induce hepatic insulin resistance in the basal state, with impaired insulin-mediated suppression of glycogenolysis as a consequence. Along the same line, reduction of FFAs by nicotinic acid in type 2 diabetic subjects did not lead to reduced gluconeogenesis *(167)*, and net HGP was increased owing to absence of induction of the glycogenolytic pathway. Thus, altered hepatic auto-regulation was paralleled by, and likely owing to, impairment of insulin sensitivity.

FFAs *per se* may diminish the ability of insulin to suppress HGP (i.e., impaired insulin signaling). Several mechanisms may be involved. For instance, LCFA-CoAs accumulate in liver when increased FFA exposure is combined with inhibition of fatty acid oxidation owing to elevated malonyl-CoA *(168)*. In vitro studies suggest that accumulation of LCFA-CoA intracellularly leads to inhibition of glucokinase, inhibition or stimulation of glucose-6-phosphatase, inhibition of glycogen synthase, and stimulation of glycogen phosphorylase *(82)*. Another possibility is that LCFA-acylCoA and their esterified derivatives (DAG, ceramides) accumulate in the liver, leading to alteration in kinase (PKC-θ, -ε, -δ and -β and AMPK) regulatory cascades *(152,169)*. Alternatively, the so-called hexosamine pathway has been proposed as a nutrient-sensing regulatory pathway *(170)*. Although insulin acts directly on hepatic insulin receptors to suppress hepatic glucose production *(7)*, and hepatic insulin resistance therefore leads to impaired suppression of HGP, it is important to appreciate that insulin-mediated reduction of FFA release from adipose tissue participates indirectly in the inhibition of HGP *(8,9)*. Therefore, impaired insulin action in adipose tissue may lead to increased HGP either directly or indirectly by increasing exposure of the liver to FFAs.

In summary, FFAs increase the *de novo* synthesis of glucose by the liver. Under physiological conditions, a counter-regulatory mechanism is set up to prevent increased HGP. However, in pathological conditions, as seen in insulin resistance and type 2 diabetes, this mechanism is defective, and chronic elevation of FFAs leads to increased HGP.

### *Effects of FFAs on Hepatic Insulin Clearance*

An elevation of circulating FFA experimentally induced by an Intralipid + heparin infusion decreases hepatic insulin extraction in vivo in dogs *(162)*. Hennes et al. *(171)* showed in humans that Intralipid + heparin decreased whole body insulin clearance (which includes both hepatic and peripheral insulin extraction) during hyperglycemic clamps. We have obtained similar findings in humans *(172)* but only after prolonged Intralipid + heparin infusion. On the contrary, others failed to show changes in hepatic insulin extraction after 48 h of Intralipid + heparin infusion performed during a 48 h hyperglycemic clamp *(173)*, possibly because of different experimental protocols. The mechanism underlying the effect of FFAs on insulin clearance may involve an increase in insulin receptor internalization and decreased insulin binding via a progressive increase in PKCδ translocation *(174,175)*. The FFA-mediated reduction in hepatic insulin extraction may be viewed as an adaptive mechanism to generate peripheral hyperinsulinemia, and thus partially overcome the peripheral insulin resistance induced by FFAs. This adaptive mechanism could relieve, in part, the stress on pancreatic β-cells imposed by insulin resistance *(176)*. This is another example of co-ordinated regulation of insulin secretion, insulin clearance, and insulin action to maintain glucose homeostasis, although the mechanisms of this cross organ communication are not currently known.

### *Effects of FFAs on Hepatic VLDL Production*

Lipoprotein metabolism in insulin resistance and type 2 diabetes will be covered elsewhere in this book and has been reviewed in more detail elsewhere *(82)*. Briefly, the hypertriglyceridemia of insulin resistance and type

2 diabetes is primarily owing to VLDL overproduction, with reduced VLDL clearance playing a role in some instances. Increased FFA flux from adipose tissue acts as a driving force to increase secretion of VLDL, which is regulated by lipid substrate availability. VLDL overproduction in insulin resistance and type 2 diabetes occurs as a result of a composite set of factors over and above the increased flux of fatty acids from extrahepatic tissues to the liver, including increased hepatic *de novo* fatty acid synthesis, preferential esterification versus oxidation of fatty acids, reduced posttranslational degradation of apo B, and overexpression of MTP, the latter being an important chaperone for the assembly of apoB-containing lipoproteins in the liver and intestine *(82)*. Low HDL-cholesterol and small, dense, more atherogenic LDL are other prominent features of the insulin resistance-associated dyslipidemia, and occur in part secondary to particle compositional changes that occur in hypertriglyceridemic states *(177)*.

## *Effects of FFA and Islet Triglyceride Stores on Pancreatic β-Cells*

### Acute Effects of FFAs on Insulin Secretion

Fatty acids exert both acute and long-term effects on insulin secretion. Fatty acids are actively taken up and metabolized by β-cells, and can regulate β-cell enzymes and ion channels *(27)*. It has long been recognized that FFAs acutely (i.e., when elevated for less than about 6 to 12 hours) increase glucose-stimulated insulin secretion (GSIS) *(172,178,179)*. Conversely, acute lowering of plasma FFAs with nicotinic acid results in a reduction in basal plasma insulin in both nonobese and obese healthy, fasted individuals *(144)* and in patients with type 2 diabetes *(26,144)*. Fatty acylCoA and possibly DAGs accumulated within the β-cells may stimulate protein kinase C and stimulate exocytosis of insulin granules *(180)*. The recently discovered GPR40 receptor is highly expressed in β-cells *(181,182)* and may be involved in the FFA-mediated insulin secretion. FFAs are ligands for this cell-surface G-protein coupled receptor *(183)*, and binding has been shown to promote insulin secretion in vitro *(184–187)*. This occurs via a series of actions, from protein kinase A activation and increased AMP/ATP ratio, which antagonizes voltage-gated K+ channels, leading to opening of voltage-dependent Ca2+ channels, increasing the intracellular Ca2+ concentration, resulting in exocytosis of insulin-containing secretory granules *(185)*. Previous studies have also shown that FFA binding to GPR40 may also induce K+-ATP channel-independent mobilization of intracellular Ca2+ pool *(188,189)*.

### Chronic Effects of FFAs on Insulin Secretion

In contrast to acute exposure, prolonged intravenous infusion of a synthetic lipid emulsion infusion (>12–24 hours) results in reduced GSIS and β-cell mass in vitro *(190)* and reduced GSIS in vivo *(172,191,192)*. Several in vitro studies in β-cell lines and in rodent and human islets have subsequently confirmed that insulin secretion at high glucose concentrations is impaired in a time-dependent fashion by exposure to FFAs *(193–197)*. Islets from prediabetic ZDF rats and from fructose-fed insulin resistant rats appear to be more susceptible to this FFA-mediated desensitization of GSIS *(195,196)*. Some controversy exists, however, because basal insulin secretion at low glucose concentrations was elevated in normal rodent islets and islet cell lines in most studies *(28,193–195,198)*. Furthermore, insulin secretion at low glucose concentration is either unchanged or decreased by FFAs in islets from ZDF prediabetic rats or prediabetic OLEFT rats *(195,199)*.

β-cell lipotoxicity, a term coined by Unger in 1995, describes lipid-induced functional impairments in GSIS as well as reduction in β-cell mass, and is also linked to, but not necessarily caused by, intracellular TG accumulation *(137)*. Insulin secretion is mainly regulated by glucose through the closure of ATP-sensitive K+ channels, leading to membrane depolarization, opening of voltage-dependent Ca2+ channels, increased intracellular Ca2+ concentration, subsequent activation of kinases, and exocytosis of secretory granules. A potential mechanism lies in the stimulation by FFAs of the ATP-sensitive $K^+$ channels *(200,201)* leading to impaired mitochondrial function. Ongoing accumulation of FFAs may chronically prevent $K^+$ channels from closure, thus contributing to the resistance. Intracellular stores of triglycerides can be hydrolyzed by hormone-sensitive lipase, which is expressed and active in β-cells *(202)* and, therefore, may constitute an additional *in situ* supply of long-chain fatty acids. FFAs may induce expression of uncoupling protein(UCP)2, thus decreasing the ATP pool generated from glucose, and insulin secretion *(203)*. Although no amelioration has been seen after adenovirus-mediated UCP-2 overexpression in β-cells derived from Zucker diabetic rats *(139)*, UCP2 expression is increased in animal

models of type 2 diabetes *(204–206)*. Fatty acid accumulation causes induction of oxidative stress *(197,207)* via elevated synthesis of ceramides, which in turn induce the expression of the inducible NO synthase iNOS *(208)*. Superoxide radical, which been shown to activate UCP2, is increased in β-cells from diabetic mice *(206)* and Zucker diabetic rats *(209)*. NO and oxygenated free radicals activate some caspases responsible for apoptosis, thus leading to reduced β-cell mass *(207,210–212)*.

An alternative hypothesis has been proposed in which FFAs may modulate the expression of certain genes involved in glucose or fatty acid metabolism. Exposure of β-cells to high levels of FFAs leads to decreased expression of the glucose transporter Glut-2 and glucokinase with subsequent decreased utilization of glucose *(213)*. In addition, FFAs decrease insulin biosynthesis *(193,214–216)*, alter proinsulin processing, and decrease insulin gene transcription by unclear mechanisms *(217,218)*. GPR40 has been suggested to mediate not only acute but also chronic effects of FFAs, because loss of GPR40 decreases insulin secretion by β-cells in response to FFAs, and GPR40-deficient mice are protected against high fat diet-induced hyperinsulinemia, hepatic steatosis, and hypertriglyceridemia, as well as increased hepatic glucose output, hyperglycemia, and glucose intolerance *(219)*. Conversely, overexpression of GPR40 results in impaired β-cell function, hypoinsulinemia, and diabetes *(219)*. FFAs-mediated downregulation of PKC or inhibition of specific PKC isoforms may also be involved.

In summary, there is convincing evidence from in vitro and some in vivo studies in animals and humans that chronically elevated fatty acids impair various aspects of pancreatic β-cell function. It is not yet known, however, whether a chronic elevation of plasma FFAs contributes to the β-cell dysfunction that is characteristic of the progression from prediabetes to type 2 diabetes in humans or how important this factor is in relation to other causative factors.

## *Effects of FFAs on Lipid Oxidation and Mitochondrial Function*

### Effects of FFAs on Muscle Lipid Oxidation and Mitochondrial Oxidative Phosphorylation

Skeletal muscle has been shown to have the capacity to switch between fat and glucose as fuel. In lean, insulin sensitive people, a switch from fasted to fed state is reflected by a pronounced decrease of FA uptake and oxidation whereas glucose is preferentially used as substrate. This capacity has been termed "metabolic flexibility" *(220)*, compared to the "inflexibility" of insulin resistant muscle to make this transition. In obese persons, fasted muscle metabolism is characterized by partially blunted fat oxidation and less suppression of glucose oxidation, and the switch to fed state is accompanied by only a slight decrease in fat oxidation and partial increase in glucose utilization *(221)*. Defects in skeletal muscle mitochondrial oxidative capacity (the process which produces ATP from fuel oxidation) and fat metabolism are correlated with, and may contribute to, insulin resistance *(220,222,223)*. In a recent study, Ukropcova *et al*. reported that insulin sensitivity was linked to the capacity of the muscle to oxidize fat, and that this relationship was retained *ex vivo* by cultured myocytes *(224)*.

Studies have linked defects in mitochondrial oxidative phosphorylation and insulin resistance in elderly subjects and in healthy individual with family history of type 2 diabetes *(123,124)*. In both cases, defects in insulin-stimulated muscle glucose metabolism were associated with lipid accumulation within the muscle, and with markedly reduced muscle mitochondrial ATP synthesis and tricarboxylic acid flux, reflecting altered mitochondrial oxidative and phosphorylative capacity. Another report has shown reduced mitochondrial size in obese, insulin resistant subjects with or without type 2 diabetes *(222)*. Two mechanisms have been invoked to explain these mitochondrial defects, which include mitochondrial dysfunction and a loss of mitochondria, potentially owing to impaired biogenesis. PGC1 (PPARγco-activator 1) is a transcription factor known to control the adaptative thermogenesis process in muscle to enhance mitochondrial oxidative phosphorylation, and is involved in mitochondrial biogenesis *(225)*. Interestingly, expression of PGC1α and/or β is reduced in obese Caucasian subjects with glucose intolerance and type 2 diabetes *(226)*, and in obese diabetic and overweight nondiabetic Mexican-Americans *(227)*. Forced expression of PGC1α in muscle leads to increased oxidative type I muscle fibers and expression of mitochondrial markers *(228)*. Conversely, PGC1α-deficient mice have lower mitochondria number and respiratory capacity, but normal mitochondrial function, and impairment of muscle PGC1α signalling may contribute to systemic insulin resistance *(229)*. Interaction between PGC1α and other transcription factors, including the estrogen-related receptor (ERR) and PPARα *(230,231)*, may also be involved in the upregulation of muscle mitochondrial oxidative phosphorylation and FA oxidation, and inhibition of glucose oxidation *(232)*. However,

when fed a high-fat diet, PGC1α-deficient mice are protected against insulin resistance, despite impairment in skeletal oxidative phosphorylation, an observation which may be explained by the fact that PGC1α may have deleterious effects in other organs, such as liver, where it potentially increases HGP, and β-cells, where it may decrease GSIS by impairing ATP-sensing $K^+$channel activity *(232)*. Further studies are awaited to delineate the role of these nuclear receptors and co-factors in linking fat metabolism and mitochondrial function.

Decreased mitochondrial fatty acid oxidation, caused by mitochondrial dysfunction or biogenesis, may generate increased intracellular fatty acyl CoA and DAGs which, in turn, impair insulin signalling via altered IRS phosphorylation and PI3K activity, leading ultimately to altered glucose uptake. Conversely, elevated FFAs may amplify this defect by directly or indirectly impairing mitochondrial function or activity of transcriptional factors involved in mitochondrial function and biogenesis. For instance, lipid infusion to raise plasma FFA concentration in healthy men during hyperinsulinemic clamp conditions leads to decreased insulin-stimulated ATP synthesis and concomitant insulin resistance *(233)*. On the other hand, FFAs have been shown to decrease PGC1 expression and mitochondrial oxidative phosphorylation (also named OxPhos) *(234)*. These results were corroborated by the report from Sparks and colleagues showing that, after 3 days, feeding a high fat diet to humans led to decreased muscle PGC1 and OxPhos gene expression *(235)*. It remains, however, to be determined whether chronic elevation of FFA in humans results in the same defects.

#### Effects of FFAs on Pancreatic β-Cell Mitochondrial Function

In line with the above data, it has become clear that mitochondrial function is also required for pancreatic β-cells to secrete insulin in response to glucose, and increased β-cell mass is necessary to respond to the increased demand for insulin. As discussed above, increased ATP/AMP ratio within the β-cells triggers a series of events, involving K+-ATP-dependent channels and Ca2+ voltage-dependent channels, leading to exocytosis of insulin secretory granules. It is therefore possible that, based on what is observed in the muscle, impaired mitochondrial function may impede glucose-stimulated insulin secretion. In support of this hypothesis, FFAs may induce expression of the mitochondrial inner membrane protein UCP2 that uncouples glucose oxidative metabolism from ATP synthesis, thereby decreasing the ATP pool generated from glucose and impairing insulin secretion *(203)*.

### *Effects of FFAs on local and systemic inflammation, and link to insulin resistance*

Elevated FFAs cause ectopic lipid deposition in nonadipose tissue, and this lipotoxicity may induce a pro-inflammatory response, which in turn may negatively interfere with insulin signalling. Supporting this concept, the use of high dose salicylate has been proven to decrease plasma glucose in type 2 diabetic patients *(236)*. The molecular basis of this observation relies on decreased activity of a serine kinase called IκB kinase β (IKKβ) of the NFκB signalling pathway *(237)*, and subsequent impaired phosphorylation of IRS-1 and PI3Kinase *(238)*. The link between IKKβ and FFAs in insulin resistance has been further supported by the report that, in rats, salicylate prevents the deleterious effects of lipid infusion on muscle glucose metabolism and insulin secretion *(238)*. In a recent report Cai and colleagues showed that obesity- or high fat-induced hepatic lipid deposition is accompanied by increased NFκB activity in the liver *(239)*. Studies of genetically modified mice with either silencing or activation of the NFκB pathway specifically in the liver demonstrated that inflammation owing to moderate hepatic NFκB overexpression may cause hepatic as well as systemic insulin resistance, whereas mice with reduced NFκB activity were resistant to the development of insulin resistance *(239,240)*. Several hypotheses exist to explain how increased FFA delivery and ensuing intracellular acylCoA and DAGs may alter IKKβ activity. One of them involves the activation of the protein kinase PKC θ *(169,241,242)*. The other one relies on fatty acid-induced alteration in another signalling pathway, named c-Jun amino-terminal kinase (JNK) pathway that can interfere with insulin action, and the activity of which is abnormally high in diabetes and obesity *(210,243,244)*. To summarize, this pro-inflammatory state appears to be an integral component of insulin resistance *(245)*, and may be in part a consequence of lipid accumulation in adipose and nonadipose tissue, through altered IKKβ activity.

Adipose tissue is also able to secrete pro-inflammatory chemokines, the secretion of which is even more pronounced in insulin resistant states, with deleterious consequences on insulin action in adipocytes *(246)*. A very recent report points to the possibility of an enhanced recruitment of monocytes to adipose tissue as a key factor for adipose tissue macrophage accumulation, an inflammatory state, and more generally systemic insulin resistance

*(247)*. It remains to be determined whether lipid overaccumulation may initiate the inflammatory response leading to monocyte/macrophage homing.

## INHIBITION OF FATTY ACID FLUX FROM ADIPOSE TISSUE. IS IT EFFECTIVE IN AMELIORATING THE MANIFESTATIONS OF INSULIN RESISTANCE AND TYPE 2 DIABETES?

As outlined throughout this chapter, prolonged exposure to elevated FFAs contributes to insulin resistance and to the many metabolic manifestations of the insulin resistant state and type 2 diabetes. It follows, therefore, that a sustained reduction in FFA flux from adipose tissue would theoretically be predicted to result in improvement in the metabolic abnormalities. Therapies that directly or indirectly improve insulin sensitivity, such as weight reduction, exercise, oral hypoglycemic agents, and insulin, are indeed associated with a reduction in FFAs and improvement in many of the metabolic disturbances of insulin resistance and type 2 diabetes, but the exact mechanism of improvement may or may not be a consequence of the reduction in FFAs *per se*. More specific therapies that primarily target abnormalities of FFA metabolism would need to be tested to address the hypothesis that reduction of plasma FFAs improves insulin sensitivity and its associated metabolic abnormalities.

The antilipolytic agent nicotinic acid and its longer acting analogues have been used to investigate the metabolic and clinical effects of reducing FFAs *(248,249)*. Acute administration of the long-acting nicotinic acid analog, acipimox, has been shown by numerous investigators to reduce plasma FFAs, fatty acid oxidation, and gluconeogenesis, and to increase glucose oxidation rates, with some but not all studies showing suppression of endogenous glucose production, increased insulin-mediated suppression of glucose production, insulin-mediated glucose uptake, and decreased intramuscular LCFA-CoA content *(250–256)*. In addition, the lipoprotein profile is modified to a less atherogenic one (reduced VLDL particle production, increased LDL particle size, lowered plasma TGs and elevated HDL-cholesterol) in hyperlipidemic patients. Insulin secretion was potentiated within one week of acipimox treatment *(257)*. Nicotinic acid and analogs act through a newly discovered G-protein coupled "nicotinic acid" receptor, which is expressed in adipose tissue and also in macrophages. Their HDL-cholesterol raising properties may be owing to additional effects on the ABCA1-mediated cholesterol efflux from peripheral tissues and its transport back to the liver. There is, however, an escape from the beneficial effects of acipimox and a rebound elevation of FFAs, which occurs with prolonged acipimox treatment and limits its potential therapeutic benefit *(164,250)* .

The insulin sensitizing PPARγ activators thiazolidinediones (TZDs) have been successfully used in the management of type 2 diabetes *(258)*. They ameliorate muscle and liver insulin sensitivity, and have been suggested to improve β-cell function. Despite an overall increase in adiposity, they induce a beneficial fat redistribution from visceral to subcutaneous fat depots, and the differentiation of new insulin-sensitive adipocytes *(259)*. Preliminary studies have also demonstrated a reduction in liver fat, with consequent improvements in hepatic inflammation and fibrosis *(260)*. The effects of TZDs on plasma fasting FFAs are variable in humans (more consistently decreased in animals), being decreased by 20-25% in some studies *(261–263)*, but barely lowered despite insulin sensitization in another *(264)*. In the latter, postprandial FFAs were decreased by TZD treatment. TZDs also increase plasma adiponectin levels, suppress the release of pro-inflammatory cytokines, and exert other pleiotropic effects directly at the level of the vascular wall *(265)*. PPARα is expressed at higher levels in tissues exhibiting high rates of fatty acid β-oxidation, i.e., muscle and liver. PPARα activation decreases plasma TGs and FFAs, partly via enhanced fatty acid uptake and oxidation by the liver. Therefore, PPARα/γ co-agonists may have substantial advantages and offer an attractive therapeutic option. In animal models of genetically or diet-induced insulin resistance, PPARα/γ dual agonists improve glucose and lipid tolerance *(266)* and enhance insulin action *(267,268)*. They have also been shown to increase glucose stimulated insulin secretion in diabetic db/db mice *(269)*.

## CONCLUSIONS

In recent years there has been an intense focus on abnormalities of FFA metabolism in the pathophysiology of insulin resistance, its metabolic complications, and type 2 diabetes. In fact, because abnormalities of FFA metabolism can often be detected well in advance of abnormalities of glucose and carbohydrate metabolism, some

have postulated that these abnormalities are a fundamental cause of type 2 diabetes. FFAs likely play an important role in communication between organs, and signal the body's energy status to the hypothalamus. Based on the belief that elevated FFAs are both diabetogenic and proatherogenic, attempts have been made to develop specific pharmacotherapies to lower plasma FFA concentrations. We postulate that elevated plasma FFA concentration (and its downstream deleterious effects) is but one consequence of the fundamental cause of insulin resistance and type 2 diabetes, i.e., positive net energy balance and obesity that develop as a consequence of an imbalance between calorie consumption and energy expenditure, modulated at multiple levels by the genetic makeup of the individual. In fact we predict that therapies directed solely at reducing plasma FFA concentration, if they do not address the factors responsible for the positive net energy balance, are doomed to fail or could result in unintended deleterious consequences.

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# 5 Detection and Diagnosis of Type 2 Diabetes

*Adrian Vella*

***CONTENTS***



**Summary**

The diagnostic criteria for diabetes have been devised based on the association of fasting and 2h post-glucose challenge (PC) values with microvascular complications of the disease. Both fasting and PC abnormalities have been associated with increasing cardiovascular risk. Neither glycosylated hemoglobin nor serum insulin levels are adequate to serve as screening tools to diagnose diabetes. Likewise, genetic screening, although promising, is not yet able to reliably identify individuals at increased risk of developing the disease. This chapter reviews the data used to create current diagnostic criteria and explores pitfalls in the differential diagnosis of hyperglycemia.

**Key Words:** Keywords Diagnosis; type 2 diabetes; impaired glucose tolerance; fasting plasma glucose; postprandial glucose.

## INTRODUCTION

Type 2 diabetes arises out of a complex interaction between genes and the environment. Although family history is an important risk factor for the development of type 2 diabetes, individual genetic predisposition cannot be explained by a single polymorphism or mutation *(1)*. At present, the best predictors of increased diabetes risk and progression to diabetes are an elevated fasting glucose, an abnormal glucose tolerance test, obesity and evidence of impaired insulin action *(2–4)*.

The term, "diabetes," comprises a common group of heterogeneous disorders characterized by hyperglycemia. Although diagnosing diabetes that presents with microvascular and macrovascular complications poses little problem for the clinician, characterizing patients as having "early" diabetes or being in a "prediabetic" state carries important implications for the initiation of preventive strategies and lifestyle modification. It must be emphasized that the diagnostic criteria described below make no attempt to distinguish between different subclasses of diabetes and guidance as to the most appropriate treatment is discussed in other chapters. Another important reason for the establishment of diagnostic criteria is to provide a tool for epidemiological study of the incidence and prevalence of the disease, define risk factors to allow public health planning, facilitate research into its causation, and compare these across populations.

The criteria established in 1979 by the National Diabetes Data Group (NDDG) were based on a level of fasting plasma glucose (FPG) of $\geq$140 mg/dL and/or a 2-h postoral glucose tolerance test (OGTT) plasma glucose level of $\geq$ 200 mg/dL on more than one occasion *(5)*. However, because data from epidemiological studies suggested

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Table 1
Evolution of the diagnostic criteria for type 2 diabetes

| | |
|---|---|
| WHO Expert Report (1965) | **Clinical**: Subject has abnormal glucose and the symptoms of diabetes<br>**Asymptomatic**: Fasting glucose ≥ 130mg/dL<br>**OGTT**: glucose ≥ 130 mg/dL 2 h after a 50 g or 100 g oral glucose challenge |
| National Diabetes Data Group (1979) | **Clinical**: Subject has abnormal glucose and the symptoms of diabetes<br>Fasting glucose ≥ 140 mg/dL on more than one occasion<br>**OGTT**: glucose ≥ 200 mg/dL 2 h after a 75 g oral glucose challenge (or any time point in between) |
| WHO (1980) | Symptoms, complications or a random glucose ≥ 200 mg/dL or a fasting glucose ≥ 140 mg/dL. Diabetes is excluded if random glucose < 140 mg/dL and fasting < 100 mg/dL<br>**OGTT**: glucose ≥ 200 mg/dL 2 h after a 75 g oral glucose challenge. 2 h-glucose < 140 mg/dL is normal and 140–200 mg/dL = glucose intolerance |
| American Diabetes Association (1997) | One of 3 criteria: -<br>Symptoms + random glucose ≥ 200 mg/dL<br>Fasting glucose ≥ 126 mg/dL on more than one occasion<br>Glucose ≥ 200 mg/dL 2 h after a 75 g oral glucose |

that the level of fasting plasma glucose (FPG) associated with an increased risk of developing microvascular complications in diabetes is closer to 126 than to 140 mg/dL, and because a FPG of 126 mg/dL has a sensitivity for diagnosing diabetes that is similar to a 2-h value of 200 mg/dL, the American Diabetes Association (ADA) in 1997 recommended that the FPG used to diagnose type 2 diabetes be changed from 140 to 126 mg/dL *(6)*. Of note, the 1999 World Health Organization (WHO) revised criteria for the diagnosis and classification of diabetes *(7)* differ little from those recommended by the ADA in 1997. The WHO report suggested that the 2-h oral glucose tolerance test (OGTT) was superior to the use of fasting glucose for epidemiological studies because of the difficulty in ascertaining that participants are truly fasting. Table 1 summarizes the evolution of the diagnostic criteria for diabetes.

## HYPERGLYCEMIA AND VASCULAR RISK IN POPULATIONS

The choice of 200mg/dL as the diagnostic threshold for the 2-h plasma glucose (2hPG) has been justified because the prevalence of the microvascular complications considered specific for diabetes (i.e., retinopathy and nephropathy) increases dramatically beyond this value *(8)*. Cross-sectional and longitudinal observations in Pima Indians *(9)*, and in the Bedford *(10)* and Whitehall *(11)* studies in the United Kingdom, showed that nephropathy and retinopathy occurred almost exclusively in subjects with a 2-h glucose value > 200 mg/dL.

These findings were confirmed in similar studies in which the FPG and 2hPG were each strongly and equally associated with retinopathy *(12–14)*. For both the FPG and the 2 h PG, the prevalence of retinopathy was markedly higher above the point of intersection of the 2 components of the bimodal frequency distribution (FPG = 129 mg/dl and 2 h PG = 207 mg/dl) (Fig. 1). The relationships of FPG and 2hPG to the development of retinopathy, evaluated in Pima Indians over a wide range of plasma glucose thresholds, produced similar results *(15)*. Both variables were similarly associated with microvascular complications, indicating that by this criterion, each could work equally well for diagnosing diabetes *(9)*. However, the inconsistency between the diagnostic criteria (FPG > 140 mg/dL and a 2 h PG of > 200 mg/dL) and the fasting and 2-h glucose values that predicted risk of microvascular complications was part of the rationale for lowering the FPG criteria for the diagnosis of diabetes in 1997.

One problem with the OGTT is the significant variability and lack of reproducibility of the test. This is especially true in subjects classified as having impaired glucose tolerance (IGT), defined as 2-h glucose < 200 mg/dL but > 140 mg/dL. Up to 75% of such subjects retested within 3 mo change their classification *(16)*. Indeed some authors have challenged the existence of impaired glucose tolerance as a discrete category, suggesting that

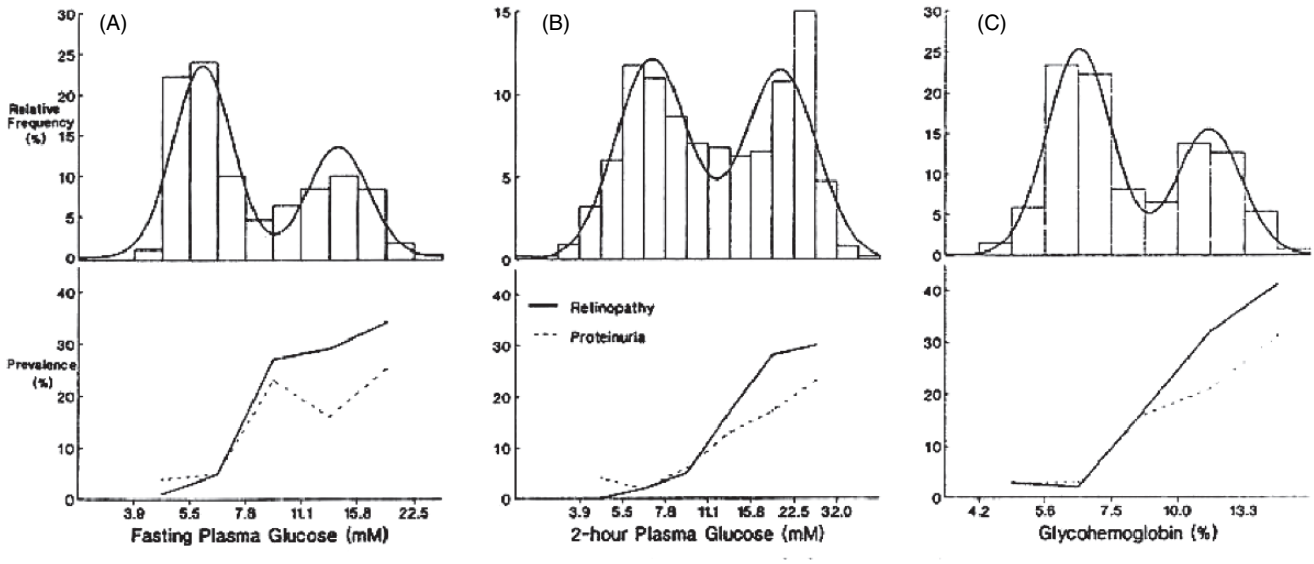


**Fig. 1.** Frequency distributions of fasting plasma glucose (Upper panel, A), 2-h plasma glucose (Upper panel, B) and $HbA_{1c}$ (Upper panel, C) in subjects > 35 yr of age. The bars show frequencies by intervals, equally spaced on a logarithmic scale. The smooth curves represent a model of 2 overlapping distributions with a common variance that was fit by maximum likelihood. The lower panels represent the prevalence of retinopathy and heavy proteinuria in the same subjects. Modified from *(12,15)*.

this may include subjects with a spurious elevation in glucose values or subjects transitioning to type 2 diabetes *(17)*. The variability of the OGTT has to be borne in mind when reviewing studies associating glucose intolerance with vascular disease *(18)*.

Although the 1997 ADA criteria emphasize FPG, some data suggest that the 2-h glucose value after OGTT is a better predictor of vascular risk than is the fasting glucose level. Several studies have shown that the 2hPG value is predictive of all cause, cardiovascular, and coronary mortality *(19–22)*. Some studies have used the criteria defined by the WHO and ADA to examine this association. Other studies such as the Paris Prospective Study analyzed the 2-h glucose concentration as a continuous variable to show that it predicted death by all causes and by ischemic heart disease *(23)*. However, this effect was not significant if adjusted for triglycerides and fasting insulin *(24)*. More recently, Balkau et al reanalyzed the data to examine the role of the fasting glucose in determining the predictive power of the 2 h PG value. In men with a fasting glucose > 126 mg/dL, 2 h PG was not predictive of all-cause mortality. However, this was not the case in men with a fasting glucose in the normal or impaired range, where this relationship was preserved *(25)*.

Other studies have prospectively examined the relationship of ischemic heart disease to glucose in nondiabetic populations. The Hoorn study reported that only the 2 h PG value was predictive of cardiovascular and all-cause mortality *(26)*. The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) Study showed a convincing trend for all-cause mortality across both fasting and 2 h PG categories. Multivariate regression analysis showed that inclusion of fasting glucose values did not add significantly to the predictive power of 2-h glucose values. The opposite was also true, with the addition of 2 h PG values significantly increasing the predictive value of fasting glucose to determine all cause and cardiovascular mortality. The greatest amount of excess mortality was observed in subjects with impaired glucose tolerance but normal fasting glucose. Such subjects tended to be older than subjects with elevated fasting glucose values and normal glucose tolerance *(27)*.

The contribution of isolated postprandial hyperglycemia to cardiovascular risk is still uncertain, although overall the evidence from more recent studies such as the Rancho Bernardo Study suggests that fasting and 2 h PG levels below the diagnostic threshold for diabetes confer increased cardiovascular risk *(28)*. However, the value of preventative strategies in this group is uncertain.

## FPG AND 2hPG FOR PREDICTING DIABETES

Glucose concentrations in nondiabetic individuals rarely exceed 140-150 mg/dl following food ingestion. This is because even a slight increase in glucose produces a prompt increase in insulin. The coordinated rise in insulin and glucose (together with a fall in glucagon secretion) suppresses endogenous glucose release and stimulates glucose uptake that, in turn, minimizes any further rise in glucose concentration. In contrast, carbohydrate ingestion results in marked and sustained hyperglycemia in people with diabetes. There are several possible reasons why this may occur *(29)*. Insulin secretion is both decreased and delayed in type 2 diabetes. Furthermore, people with type 2 diabetes exhibit defective insulin action (i.e., the ability of insulin to stimulate glucose uptake and suppress glucose release).

Numerous studies have demonstrated that either of these abnormalities have the potential to alter glucose tolerance. However, although insulin secretion varies from individual to individual, the pattern of change in postprandial insulin concentrations is remarkably consistent by the time frank hyperglycemia develops. Several studies have also established the importance of the timing of insulin secretion on glucose tolerance, so that for any given glucose challenge, a delay in insulin delivery results in a greater increment in plasma glucose concentration.

For example, Basu et al demonstrated that defects in insulin action had a different temporal effect on glucose tolerance than did altered insulin secretion. A decrease in insulin action minimally affected peak glucose concentrations, but markedly prolonged the duration of hyperglycemia. The investigators showed that concurrent defects in the pattern of insulin secretion and action caused a greater deterioration in glucose tolerance than either alone *(30)*.

Several studies have confirmed that the level of FPG is a major determinant of an individual's subsequent risk of developing diabetes. In addition, the risk of diabetes increases with the degree of elevation of the FPG level, even among individuals with a FPG level within the "normal" range *(31)*. A longitudinal, population-based study by Dinneen et al showed that the main effect of altering FPG diagnostic criteria for type 2 diabetes was an earlier diagnosis of the disease *(32)*. This is consistent with observations based on NHANES III data *(33)*. Pooled data from 6 cohort studies, involving 16,775 person-years of follow-up, showed that the level of FPG, the 2-h post-OGTT glucose, and the baseline BMI were the most important predictors of progression from impaired glucose tolerance to diabetes *(34)*. In that dataset, there was an increasing incidence of diabetes from the lowest to the highest quartile of FPG.

People with impaired fasting glucose (FPG 110 to 124 mg/dL) have an approximatley 6-fold higher risk of progressing to a FPG >126 mg/dL compared with individuals with initial FPG < 100 mg/dL. Although this subgroup is at low risk of progressing to diabetes, it contributed the largest number of individuals who went on to develop diabetes of all subgroups. This observation is relevant to the planning of population-based diabetes prevention strategies that must target a population not necessarily identified on the basis of glucose values as being at risk of developing diabetes in the future *(32)*.

## OTHER POTENTIAL SCREENING METHODS

### *Glycosylated Hemoglobin*

Nonenzymatic attachment of glucose to the hemoglobin chain has long been used as a measure of metabolic control in diabetes. Both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have validated the link between hemoglobin glycosylation and microvascular complications. Given the pitfalls of screening based on fasting glucose and OGTT values, and the fact that the OGTT is a cumbersome test to use in clinical practice, the use of glycated hemoglobin has been explored as a screening and/or diagnostic test for diabetes.

The Islington Diabetes Survey was designed to evaluate the use of glycated hemoglobin as a screen for diabetes in a random selection of patients from a primary care practice in London. The glucose tolerance of participants was determined by means of a 75 g OGTT. Thirteen of 223 subjects had diabetes and 48 had IGT. Receiver-operating characteristic curves showed poor accuracy of glycosylated hemoglobin as a screening test for any degree of glucose intolerance *(35)*.

In the Early Diabetes Intervention Program (EDIP), 101 subjects in whom the 2 h post-OGTT glucose value exceeded 200 mg/dL, 45% had a fasting glucose > 126 mg/dL. In contrast, 62% had an $HbA_{1c}$ value greater

than 2 standard deviations above the mean (> 6.1%), i.e., this test would have detected 17% more patients with diabetes than fasting glucose values alone *(36)*.

### *Insulin*

Fasting hyperinsulinemia has been used as a surrogate marker for insulin resistance. The caveats associated with the diagnosis of the "metabolic" or "insulin resistance" syndrome are discussed briefly below. In a feedback loop, all hormone concentrations must be interpreted in light of the concentrations of their regulatory target. Butler et al have pointed out that although patients with type 2 diabetes have higher fasting insulin concentrations than people without diabetes, these concentrations are inappropriately low for the prevailing fasting hyperglycemia *(37)*. Although hyperinsulinemia may imply defective insulin action, the high insulin concentrations are not directly causative of the adverse cardiovascular risk seen in such situations. Vide the absence of excess vascular risk in patients with high insulin concentrations due to insulinoma *(38)*.

### *Genetic Screening*

Unlike syndromes akin to maturity onset diabetes of the young (MODY) in which families have an affected proband who may fit the criteria of the syndrome *(39)*, genetic analysis has little role to play in the detection of people at risk for type 2 diabetes. Although studies in monozygotic and dizygotic twins have suggested a high genetic contribution to the development of type 2 diabetes, the environment plays a large role in determining the development of the disease. This is demonstrated by a measure of heritability, the $\lambda_s$ ratio, which is the ratio of sibling risk (siblings of affected individuals) to population risk. Mendelian disorders such as MODY or cystic fibrosis have a $\lambda_s$ ratio $\gg$ 100, in contrast to disorders with no genetic contribution where the $\lambda_s$ ratio is 1. For type 2 diabetes, $\lambda_s$ ratio is $\sim$ 5. The data available so far suggest that the genetic predisposition to type 2 diabetes is conferred by multiple, common genetic variants with weak effect (relative risk conferred by disease-associated allele < 1.5). A few loci have been accepted as conferring risk for developing the disease. In the case of a common polymorphism causing an amino acid change in the protein encoded by *PPARG*, (the gene encoding the peroxisome proliferative activated receptor gamma – the drug target for thiazolidinediones) the disease-associated allele is actually the commoner allele in Caucasian populations *(40)*. The allele frequency of the disease-associated alleles in unaffected individuals and comparison of allele frequencies in case-control studies will rapidly illustrate that these variants alone have little role in assigning disease risk to individual patients *(1,41)*.

## DIABETES IN SPECIAL CIRCUMSTANCES

Hyperglycemia in acutely ill patients is associated with increased morbidity and mortality. It has been shown to be an adverse prognostic factor in myocardial infarction *(42)*. The relationship with outcome is less certain in the intensive care setting *(43)*. Hyperglycemia has been associated with an increased risk of infection and wound breakdown, among other complications *(44)*. At least one study has suggested that intensive glycemic control improves measures of morbidity and mortality in the postsurgical intensive care setting *(45)*. Reductions in mortality have not been shown in myocardial infarction, during coronary bypass *(46)*, or in the medical intensive care setting *(47)*.

The long-term implications of hyperglycemia in the acute setting remain undefined. The persistence of abnormal plasma glucose concentrations identified while a patient is receiving inotropes or corticosteroids etc. during acute illness may to a certain extent be determined by previous underlying metabolic abnormalities or a genetic/environmental predisposition to diabetes. A prospective cohort study of 100 patients admitted to a medical intensive care unit concluded that $HbA_{1c}$ was an independent predictor of peak and average glucose concentrations *(48)*. In another study, 181 patients admitted to a coronary care unit in Sweden concluded that persistence of abnormal glucose tolerance at 3 mo postinfarction was to a certain extent predicted by admission $HbA_{1c}$ *(49)*. Appropriate follow up for acutely hyperglycemic patients is poorly defined but evaluation with a fasting glucose and $HbA_{1c}$ 3 mo after dismissal may be reasonable.

Poorly controlled diabetes, as with all significant systemic illnesses, can cause hypothalamic-pituitary dysfunction. Consequently, menstrual and ovulatory disturbances have long been associated with inadequate

glucose control. Another disease process that has been associated with type 2 diabetes and menstrual disturbances is polycystic ovary syndrome (PCOS). This syndrome is characterized by hyperandrogenism and oligomenorrhea with or without the presence of polycystic ovaries. A correct diagnosis requires the exclusion of other causes of hirsutism and menstrual disturbances *(50)*. Although the diagnostic criteria for PCOS do not include metabolic disease, this syndrome has been increasingly associated with "metabolic syndrome" and adverse cardiovascular risk *(51)*.

The topic of the metabolic syndrome has been a subject of controversy in the literature. Risk factors for cardiovascular disease tend to cluster in the same individual(s), and include type 2 diabetes, obesity, hyperlipidemia and hypertension. Several authors have postulated that insulin resistance, characterized by compensatory hyperinsulinemia seen in many of these individuals, may be the underlying pathophysiological defect that leads to adverse cardiovascular risk. Others have suggested that the hyperandrogenism and oligomenorrhea encountered in PCOS are caused by insulin resistance, raising the possibility that metabolic syndrome and PCOS are different facets of the same disease *(52)*.

Kahn et al have recently demonstrated the lack of clearly defined criteria (and different criteria propounded by different institutions, e.g., the World Health Organization versus the National Cholesterol Education Program) for definition of the metabolic syndrome *(53)*. Furthermore, there is no evidence to support the suggestion that the hyperinsulinemia accompanying defective insulin action directly causes vascular disease or confers the adverse cardiovascular risk seen in the metabolic syndrome. Indeed patients with high circulating insulin levels as a primary abnormality (owing to islet tumor-induced dysregulation of insulin secretion) do not have the accompanying features of the metabolic syndrome *(38)*.

## DIFFERENTIAL DIAGNOSIS OF HYPERGLYCEMIA

Just as the emergence of type 2 diabetes presenting as hyperglycemia in obese children and adolescents has emphasized that type 2 diabetes can occur at any age, it is imperative to remember that not all asymptomatic hyperglycemia is owing to type 2 diabetes. Some disorders may produce defects in insulin secretion and action akin to those observed in type 2 diabetes and may also result in "unmasking" of an innate predisposition to the disease. Indeed, in these cases hyperglycemia does not always resolve with treatment of the underlying disorder.

Acromegaly results from growth hormone (GH) excess and is frequently associated with hyperglycemia or frank diabetes. GH impairs insulin action, and people with overt diabetes in the setting of acromegaly also have severe impairment of insulin secretion. This defect may not correct completely even after cure of the disease has been affected. The disease has a subtle and insidious onset, and impaired fasting glucose may be an early manifestation that could prompt detection and diagnosis of GH excess. Somatostatin analogues are commonly used as second line therapy to control GH secretion; these medications impair insulin secretion. However, in general their beneficial effects on the disease process usually outweigh the adverse effects on insulin secretion, improving overall glycemic control *(54)*.

Glucocorticoid excess, whether from endogenous or exogenous sources, decreases insulin action and directly increases hepatic glucose production through enhanced gluconeogenesis. Glucocorticoids also stimulate hormone sensitive lipase, enhancing lipolysis. Unsurprisingly, there is a high incidence of impaired glucose tolerance and impaired fasting glucose as well as overt diabetes in this setting. Distinguishing an obese patient from a Cushingoid patient may not be a trivial task, as striae, supraclavicular fat pads, etc. may all be present *(55)*. A Cushingoid appearance may also result from use of protease inhibitors, used to treat infection with human immunodeficiency virus (HIV). These medications may produce a lipodystrophic syndrome: proximal muscle and limb wasting is accompanied by a buffalo hump, hypertriglyceridemia, and diabetes or glucose intolerance *(56)*.

Ongoing therapeutic use of steroids or incomplete cure may preclude resolution of the hypercortisolemic state. However, even when cure of Cushing's disease or Cushing's syndrome is achieved, glucose intolerance or diabetes may not resolve. This may be owing to the underlying predisposition to diabetes "unmasked" by the steroid excess or the weight gain caused by the disease process.

Hemochromatosis is a diagnosis that should be considered in all patients (especially males) with impaired fasting glucose especially if it occurs in the setting of cardiomyopathy or primary hypogonadism. Phlebotomy may be beneficial but will not reverse the acquired defect of pancreatic endocrine secretion.

**Table 2**
**Medications associated with hyperglycemia**

| | |
|---|---|
| Antihypertensive medication | β-Blockers |
| | Thiazides |
| Antiviral therapy | Interferon |
| | Protease inhibitors |
| Atypical Antipsychotics | Clozapine |
| | Risperidone |
| | Olanzapine |
| Others | Corticosteroids |
| | Niacin |
| | Pentamidine* |
| | Somatostatin |

*Pentamidine administration is associated with acute hypoglycemia followed by hyperglycemia owing to direct islet toxicity.

Numerous medications have been associated with worsening of carbohydrate homeostasis *(57)*. Table 2 provides a partial list of common medications known to worsen glucose tolerance. Somatostatin and protease inhibitors have already been mentioned. It is important to consider the possible contribution of all suspect medications to the rise in patients' fasting glucose concentrations before any specific pharmacologic intervention.

Maturity Onset Diabetes of the Young (MODY) is a heterogeneous group of disorders characterized by diabetes transmitted in an autosomal dominant fashion, typically presenting in young, nonobese adults who usually secrete insulin and are ketosis resistant. Mutations in at least 7 genetic loci have been shown to cause this syndrome. Interestingly, a subset of affected individuals experience a marked beneficial response to treatment with sulfonylureas as opposed to insulin sensitizers or insulin *(58)*.

Not all patients with elevated fasting glucose have type 2 diabetes. Type 1 diabetes may also present at any age and should be considered in the differential diagnosis, especially if the affected individual is relatively fit, nonobese, and has no family history of type 2 diabetes. There is no good test to distinguish immune-mediated diabetes from other forms of diabetes —he absence of autoantibodies does not preclude the diagnosis while their presence in low titre may be nonspecific *(59)*. The glucagon stimulation test may not be useful to diagnose type 1 diabetes in the earlier stages of disease, when endogenous secretion is likely to be preserved *(60)*.

## THE FUTURE

The ideal of accurately identifying the predisposition to diabetes in individual patients and intervening in a fashion targeted at the underlying pathophysiological processes is not yet possible. However, this is not as far-fetched as it seems. A few genetic loci have been reproducibly associated with type 2 diabetes. For example, the common, disease-associated variant in *PPARG* increases the risk of type 2 diabetes (RR ~1.2) and could conceivably alter insulin action, thereby predisposing to the disease. Similarly, a variant in *KCJN11*, the target for sulfonylureas (RR of ~1.4), may alter insulin secretion. At the present time, given the weak effect of such polymorphisms on disease predisposition, their frequency in the population, and our lack of understanding or the interaction of such variants with the environment to produce diabetes, predicting individual genetic risk of type 2 diabetes is not possible. However, efforts to understand the genetic predisposition to diabetes are underway, as are studies examining the interaction of disease-associated variants to produce disease. In the future it may be possible to determine individual genetic risk so as to help guide appropriate intervention.

At the present time, intervention studies have clearly shown that it is possible to decrease the risk of progression to type 2 diabetes. Lifestyle intervention has been shown to be safe and effective and is clearly the safest and most powerful intervention available to physicians at the present time *(61)*. Our future challenge is to correctly identify individuals at risk and intervene appropriately.

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# 6 Therapies for Delay or Prevention of Type 2 Diabetes

*Mary Angelyn Bethel*

***CONTENTS***



**Summary**

As the epidemic of type 2 diabetes continues to grow, efforts to define effective diabetes prevention strategies are gaining momentum. Although lifestyle interventions have consistently been shown to reduce diabetes incidence, difficulties with long-term adherence and contraindications owing to concomitant morbidity associated with diabetes make pharmacological prevention strategies an attractive option. Oral antidiabetic agents, antiobesity agents, lipid lowering drugs, and antihypertensive medications have all been implicated in diabetes prevention. However, few studies have provided sufficient follow up to determine if noted reductions in diabetes incidence associated with the agents represent prevention or delay of the disease. Additionally, whether reducing diabetes incidence will subsequently translate to lasting benefits in morbidity and mortality remains unclear.

**Key Words:** Type 2 diabetes; diabetes prevention; metformin; acarbose; tolbutamide; thiazolidinedione; nateglinide; ACE inhibitor; angiotensin receptor agonist.

## INTRODUCTION

The epidemic of type 2 diabetes continues to grow worldwide. Current estimations are that 171 million individuals are currently affected and that the number of cases may double by 2030 *(1)*. In the U.S. alone, diabetes was responsible for an estimated $132 billion in direct and indirect costs in 2002 *(2)*. As the costs of medical care continue to escalate, placing an ever increasing burden on global healthcare systems, the development of effective strategies for diabetes prevention has become of great interest.

Type 2 diabetes is the culmination of progressive insulin resistance and pancreatic beta-cell dysfunction. Data from the United Kingdom Prospective Diabetes Study (UKPDS) indicates both may be impaired as much as 10 yr before the diagnosis of diabetes *(3)*. Before glucose abnormalities sufficient to meet the diagnostic criteria for diabetes appear, there exists an interval, called prediabetes, either in the form of impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). Isolated IFG is defined as FPG (fasting plasma glucose) between 100 mg/dL and 126 mg/dL, whereas IGT is defined by plasma glucose greater than 140 mg/dL and less than 200 mg/dL measured 2 h after the administration of an oral glucose tolerance test (OGTT). During the interval of prediabetes, there exists an opportunity for diabetes prevention.

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Epidemiologic studies have demonstrated that prediabetes is associated with increased risk of cardiovascular events and mortality. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study demonstrated an independent association of both fasting and 2 h postchallenge (2hrPC) glucose levels with increasing all cause and cardiovascular disease mortality *(4)*. Similarly, increased cardiovascular risk has been associated with abnormal glucose metabolism, even at glucose levels currently considered to be in the normal range *(5,6)*. Although recent prospective, randomized, controlled trials (RCTs) have demonstrated that progression to diabetes can be delayed by a variety of lifestyle and pharmacologic interventions, whether this delay can be translated to reduced morbidity and mortality is unclear. Similarly, whether true prevention is feasible or whether these interventions produce merely a short-term delay of progression to diabetes remains to be proven.

Lifestyle interventions are currently considered first line therapy both for diabetes and prediabetes. A number of studies have demonstrated, primarily in subjects with IGT, that modifications in diet and exercise regimens can reduce the incidence of diabetes *(7–9)*. The most rigorous of these, the Diabetes Prevention Program (DPP) showed that intensive lifestyle modifications may decrease the incidence of type 2 diabetes by up to 58% *(9)*. The benefits of lifestyle interventions can be related to weight loss, improved diet, and improved cardiovascular fitness; however, long term adherence to these programs is low, and feasibility in nonclinical trial settings may

**Table 1**
**Placebo controlled RCTs evaluating oral hypoglycemic agents for prevention of diabetes**

| *Trial (n)* | *Population* | *F/U Length (yrs)* | *DM dx criteria* | *Intervention* | *% new DM* | *NNT* |
|---|---|---|---|---|---|---|
| BIGPRO | High waist-to-hip ratio | 1 | Self report or FPG > 140 mg/dL | Placebo | 2% | |
| | | | | metformin | 0% | 50 |
| DPP | >25 yo, BMI >24, FPG 95-125, 2h 140-199 | 2.8 | FPG>126, 2h> 200 | standard lifestyle + placebo | 28.9 | |
| | | | | standard lifestyle + metformin | 21.7 | 14 |
| | | | | intensive lifestyle | 14.4 | 7 |
| Sartor et al. | Men with IGT | 10 | 3h OGTT with all values 3 SD above the mean | placebo | * | |
| | | | | tolbutamide | * | * |
| STOP-NIDDM | 40-70 yo; BMI 25-40; 1st degree relatives with type 2 DM; IGT and IFG | 3.3 | 2h > 200 | placebo | 41.5 | |
| | | | | acarbose | 32.4 | 11 |
| TRIPOD | >18 years old, gestational DM in the prior 4 years, and sum of IGT >625 | 2.5 | FPG>126, 2h >200 | placebo | 12.3 | |
| | | | | troglitazone | 5.3 | 14 |
| DREAM | >30 yo, IGT or IFG, no known CV disease | 3 | FPG>126, 2h >200 | placebo | 10.6 | |
| | | | | rosiglitazone | 25.0 | 7 |

Abbreviations: BMI=body mass index in kg/m$^2$; DM = diabetes mellitus; FPG=fasting plasma glucose; F/U= follow-up; NNT=number needed to treat compared to placebo; IGT= impaired glucose tolerance; IFG=impaired fasting glucose; CV=cardiovascular.
*Cannot be reliably calculated due to crossover between groups.

limit their effectiveness. For individuals in whom lifestyle interventions may be insufficient or contraindicated by other comorbidities, pharmacological therapy to prevent type 2 diabetes may be a viable option (Table 1).

## ORAL HYPOGLYCEMIC AGENTS

### *Biguanides*

The sole member of the biguanide class available for clinical use is metformin. Metformin is an established agent for treatment of type 2 diabetes and has been shown to reduce hepatic glucose output and improve insulin sensitivity. The Biguanides and Prevention of Risks in Obesity (BIGPRO) trial was one of the first to examine the potential of metformin to improve the metabolic profile of patients with prediabetes *(10)*. BIGPRO enrolled patients without known cardiovascular disease or diabetes and with an elevated waist-to-hip ratio, thought to indicate the presence of insulin resistance. Subjects were randomized to 850 mg of metformin twice daily or placebo and followed for a mean of 1 yr. Among the 324 patients available for analysis, those randomized to metformin ($n = 164$) demonstrated improvements in weight loss ($-$ 2.0 kg versus $-0.8$ kg in the placebo group, $p < 0.06$), fasting plasma glucose (increased by 3.6 versus 7.2 mg/dL, $p < 0.05$), and LDL maintenance ($-0.77$ versus a 3.8 mg/dL increase in the placebo group, $p < 0.07$) at 1 yr. Rates of conversion to diabetes and cardiovascular event rates in the trial were too low to calculate an effect of metformin on these endpoints.

Because of promising results like those seen in the BIGPRO trial, metformin was selected as a treatment arm in the largest trial of diabetes prevention, the DPP *(9)*. The DPP enrolled 3234 subjects with IGT and randomized them to intensive lifestyle intervention, 850 mg metformin twice daily, or placebo. Although less effective than the 58% reduction in diabetes incidence seen in the intensive lifestyle intervention group, metformin did result in a 31% drop in progression to diabetes ($p < 0.001$ for both interventions). Both metformin and lifestyle were similarly effective at restoring normal fasting glucose values, but metformin did not differ significantly from placebo in effect on 2hr PC values or the presence of hyperlipidemia *(9,11)*.

### *Sulfonylureas (SFUs)*

Few randomized, controlled studies of SFUs for diabetes prevention have been conducted in patients with IGT. Because SFUs carry a greater risk of hypoglycemia than other oral agents, they have often been excluded from prevention trials owing to perceived imbalance between risk in this largely asymptomatic population and an, as yet, unproven benefit. However, Sartor et al did demonstrate a reduction in progression to diabetes among patients treated with tolbutamide in a cohort recruited in Sweden between 1962 and 1965 *(12)*. Patients with IGT ($n = 206$) were randomized to 0.5 g tolbutamide 3 times daily, placebo, dietary counseling only, or no intervention. After a 10 yr follow up, diabetes incidence was as follows: 29% (17 of 59) of untreated patients, 15% (18 of 124) of patients treated with diet only (including 26 patients who had tolbutamide discontinued, presumably owing to hypoglycemia, although the authors do not specify), and 0% (0 of 23) tolbutamide treated patients. Despite the seemingly marked effect of tolbutamide, the overall number of treated patients was too small to allow adequate power to determine tolbutamide's true effect.

Since the Sartor study, no other trials have been performed to examine SFU effect on diabetes prevention. Despite the development of newer SFUs with better side effect profiles (i.e., less hypoglycemia), many prevention studies continue to avoid SFU therapy owing to the imbalance of risk and benefit for patients otherwise asymptomatic from their disease.

### *Acarbose*

The only RCT of acarbose for diabetes prevention is the Study To Prevent Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM) *(13)*. STOP-NIDDM enrolled 1,368 patients with IGT who were also at otherwise high risk for the development of diabetes (i.e., first-degree relatives of patients with type 2 diabetes, body mass index [BMI] 25–40 kg/m2). Patients were randomized to receive either placebo or acarbose 100 mg 3 times daily (after dose titration designed to reduce the known gastrointestinal side-effects of acarbose). After mean follow up of 3.3 yr, 32% of patients in the acarbose group progressed to diabetes, compared to 42% in the placebo group ($p = 0.0015$). Patients in the acarbose group also demonstrated a modest weight loss (0.5 kg) compared to

modest weight gain in the placebo group (0.3 kg). However, the benefits of acarbose were persistent, even after controlling for age and BMI.

Although not originally designed to address effects on cardiovascular outcomes, subsequent analysis has demonstrated that that patients randomized to receive acarbose had a significantly reduced risk of developing any cardiovascular event, including MI, angina, cardiovascular death, CHF, stroke, and peripheral vascular disease (HR 0.51, 95%CI: 0.28, 0.95, $p = 0.03$) *(14)*. However, interpretation of this finding is limited by the small number of events (15 in the acarbose group and 32 in the placebo group), and the authors did not adjust the statistical analysis for testing of multiple hypotheses.

The use of acarbose has been limited, both in clinical practice and in STOP-NIDDM, by the prevalence of gastrointestinal side effects. Subjects enrolled in STOP-NIDDM did not reach maximum titration; the mean daily dose of acarbose was 194mg. The trial had a high rate of premature discontinuation (24%, 211 in the acarbose group and 130 in the placebo group), and the most common reason for discontinuation was gastrointestinal side effects (93 patients in the acarbose group, 18 patients in the placebo group). However, analysis of the demographic and biochemical data in the dropout population was identical to the overall study population, and 97% of those who dropped out were assessed at 3 yr for diabetes and cardiovascular endpoints. Inclusion of the drop out patients in the analysis did not significantly change the overall diabetes conversion rate for the trial.

### *Thiazolidinediones (TZDs)*

One of the first trials to examine the effect of TZDs in diabetes prevention was the Troglitazone Prevention of Diabetes (TRIPOD) study, which randomized patients to troglitazone versus placebo *(15)*. Unlike most other prevention trials, TRIPOD enrolled only women with a history of gestational diabetes and evidence of glucose intolerance. Among the 266 Hispanic women enrolled, diabetes incidence in the placebo group was 12.1%, compared to 5.4% in the troglitazone arm (HR: 0.45, 95% CI 0.25– 0.83). However, the study was limited by a significant number of patients lost to follow up; eleven women in the placebo group and 19 and the troglitazone group failed to return for any follow-up. Women who did not return had higher BMIs and lower measures of insulin sensitivity. Authors attempted to adjust the analysis by assigning the diabetes incidence rate observed in the placebo group to the group without follow-up. In that analysis, the risk reduction in the troglitazone group remained unchanged (HR 0.54, 95% CI 0.32– 0.92). Use of troglitazone was also limited by the development of liver dysfunction, a complication later leading to removal of troglitazone from the market. During TRIPOD, 9 women had study medication discontinued owing to serum transaminase concentrations more than 3 times the upper limit of normal without clinical explanation. At unblinding at study end, 6 of these 9 women had been assigned to troglitazone.

The DPP initially included a troglitazone arm, later discontinued owing to increasing concerns regarding liver toxicity and after the death of 1 DPP participant in the troglitazone group. However, despite a short exposure time (mean 0.9 yr), the lowest conversion to diabetes (3 cases/100 person-years) was seen in the troglitazone arm, representing a 75% risk reduction compared to baseline *(16)*.

The Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial is the most recent to examine the role of thiazolidinediones on diabetes prevention *(17)*. The DREAM trial randomized 5,269 subjects with IGT and/or IFG, in a $2 \times 2$ factorial fashion, to ramipril (15 mg/d) and/or rosiglitazone (8 mg/d) versus placebo. Treatment with rosiglitazone resulted in a 60% reduction in the primary composite outcome of diabetes or death (HR 0.40, 95% CI 0.35–0.46), primarily due to a 62% relative reduction in the risk of progression to diabetes (HR 0.38, 95% CI 0.33–0.44). Although the trial enrolled patients at low risk of cardiovascular disease and was not powered to provide a definitive estimate of the effect of rosiglitazone on cardiovascular outcomes, there was a trend toward an increase in risk of the cardiovascular composite outcome with rosiglitazone (HR 1.37, 95% CI 0.97–1.94), driven primarily by a significant increase in nonfatal congestive heart failure (HR 7.03, 95% CI 1.60 to 30.9, $p = 0.01$). Further concern that rosiglitazone may be associated with increased rates of MI *(18)* make the use of this drug for diabetes prevention problematic.

### *Nonsulfonylurea Secretagogues*

Agents in this class include nateglinide and repaglinide. Both are designed to address predominantly postprandial hyperglycemia. Although studied in patients with type 2 diabetes, they have not yet been evaluated in patients with

IGT for diabetes prevention. As epidemiologic evidence accumulates to demonstrate an association between 2hr PC hyperglycemia and increased cardiovascular events, even among prediabetic patients, the utility of medications targeting postprandial hyperglycemia to prevent diabetes and possibly cardiac disease becomes appealing. The ongoing Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial is the first trial designed to look simultaneously at both diabetes and cardiovascular events as co-primary endpoints in patients with IGT randomized in a 2 × 2 factorial fashion to nateglinide or valsartan. Results from NAVIGATOR, expected in 2007, may help to determine the success of nonsulfonylurea secretagogues in diabetes prevention.

## ANTIOBESITY AGENTS

Owing to the association of diabetes with obesity, the role of antiobesity agents in diabetes prevention has been investigated. The largest trial, Xenical in the prevention of Diabetes in Obese Subjects (XENDOS), analyzed the effect of 120mg orlistat versus placebo 3 times daily in 3,277 obese (BMI > 30 kg/m2) subjects *(19)*. A subgroup ($n$ = 344 in the placebo group and n = 350 in the orlistat group) also had IGT at baseline. After mean follow up of 4 yr, subjects receiving orlistat had a 37.3% reduction in the incidence of diabetes (6.2% versus 9.0% in the placebo group). Subjects in the orlistat arm also experienced a significant weight reduction over 4 yr (5.8 kg versus 3.0 kg, $p < 0.001$). Subsequent analyses revealed that the difference in diabetes incidence in XENDOS was driven primarily by patients with IGT at baseline. Among patients with normal glucose tolerance at baseline, there was no significant difference between the groups (2.7% placebo versus 2.6% orlistat). However, in those with IGT at baseline, orlistat demonstrated a 37.3% (HR 0.627, 95% CI 0.46–0.86) reduction in diabetes incidence, compared to the placebo group. Weight loss was similar in the IGT participants (5.7 kg with orlistat versus 3.0 kg) as that seen in the trial overall. Despite these promising findings, use of orlistat in clinical practice has been limited owing to gastrointestinal side effects, including oily stool, flatus with discharge, and fecal incontinence. In XENDOS, 91% of patients taking orlistat experienced gastrointestinal side effects, compared to 65% in the placebo arm, and the attrition rate for the study was 57%.

## LIPID LOWERING AGENTS

Many patients with diabetes and prediabetes also suffer from dyslipidemia, characterized by high triglycerides and low HDL. Drugs commonly used to treat dyslipidemia, including fibrates and statins, have also been demonstrated to have an effect on progression to diabetes. Although a number of mechanisms have been postulated, including enhanced glucose uptake owing to increased glucose transporter translocation mediated by statins *(20)* and improved insulin sensitivity mediated by the peroxisome proliferators-activator receptor (PPAR) alpha pathway affected by fibrates *(21,22)*, results for diabetes prevention have been inconsistent and are derived solely from post hoc analyses of cardiovascular trials.

### *Fibrates*

Although no prospective trials exist to evaluate fibrates for diabetes prevention, a posthoc analysis performed from the Bezafibrate Infarction Prevention (BIP) trial did show a difference among treatment groups *(23)*. Overall, BIP enrolled 3,122 patients with a history of prior MI or stable angina and randomized them to bezafibrate versus placebo. Although no difference was seen among groups in the primary composite endpoint (fatal MI, nonfatal MI, or sudden death), a 39.5% reduction in the primary endpoint was seen among the subgroup with high triglycerides (> 200 mg/dL at baseline). Among the 303 patients with IGT enrolled in BIP ($n$ = 147 in the placebo group, $n$ = 156 in the bezafibrate group), treatment with bezafibrate was associated with a reduction in the incidence of diabetes (54.5% in the placebo group, compared to 42.3% for bezafibrate) after mean follow up of 6 yr *(24)*.

Other posthoc analyses using fibrates have not confirmed these results for diabetes prevention. However, fibrates have a demonstrated benefit for cardiovascular event prevention among patients with features of the metabolic syndrome. In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA HIT), 3,090 patients (91% men) with documented cardiovascular disease, low HDL, and low LDL were randomized to gemfibrozil versus placebo *(25)*. In contrast to the results of BIP, the overall VA HIT showed that treatment with bezafibrate

reduced the risk of MI and cardiovascular mortality by 22%. However, a subgroup analysis of patients with insulin resistance, as defined by the homeostasis model assessment of insulin resistance (HOMA-IR: a measure of insulin resistance calculated from fasting insulin and fasting glucose values), demonstrated a selectively greater benefit of gemfibrozil in reducing cardiovascular events despite comparatively smaller increases in HDL and decreases in triglycerides *(26)*. This finding suggests that a nonlipid effect of fibrate therapy may exist; however, this finding has not been confirmed prospectively.

### *Statins*

As with fibrates, no prospective diabetes prevention trials have been conducted using statin therapy, and subgroup analyses have yielded conflicting results. Data from post hoc analyses are available for the West of Scotland Coronary Prevention Study (WOSCOPS; pravastatin versus placebo), the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA; atorvastatin versus placebo), the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID; pravastatin versus placebo), and the Heart Protection Study (HPS; simvastatin versus placebo). In WOSCOPS, treatment with pravastatin was associated with a significant reduction in nonfatal MI or cardiovascular death (31% risk reduction; 95% CI 17 to 43%) *(27)*. Among the 139 patients who transitioned from normal glucose tolerance to diabetes within the mean follow up of 5 yr, pravastatin therapy evinced a 30% relative risk (RR) reduction (95% CI 0.50 to 0.99) in progression to diabetes *(28)*.

In contrast, none of the other trials demonstrated a statistically significant reduction in diabetes incidence. LIPID *(29)* demonstrated a nonsignificant RR reduction for new diabetes in pravastatin treated patients (RR 0.89, 95% CI 0.70–1.13). Both ASCOT-LLA *(30)* and HPS *(31,32)* demonstrated a slightly increased, but nonsignificant RR for diabetes: for ASCOT-LLA, the RR was 1.15 (95% CI 0.91–1.44); for HPS, the RR was 1.15 (95% CI 0.99 to 1.34).

## ANTIHYPERTENSIVES

Although only one prospective trial designed to examine the impact of various antihypertensive therapies on the development of diabetes has been completed, a number of cardiovascular trials employing these agents have measured the resultant incidence of diabetes, either in posthoc analyses or as secondary endpoints (Table 2). However, a growing body of observational and epidemiological data indicates that there may be real differences among the antihypertensive classes in their ability to accelerate the progression to diabetes.

### *Thiazides and Beta-blockers (BBs)*

Conflicting evidence exists for the role of thiazides and BBs in progression to diabetes. One large cohort study of 76,000 Canadians utilizing administrative data concluded that the use of thiazide diuretics and BBs was not associated with incident diabetes *(33)*. However, the mean duration of follow up in the study was less than 1 yr, possibly insufficient to identify any negative effect on glycemia owing to either drug class. The Atherosclerosis Risk in Communities (ARIC) cohort, which provided sufficient follow up of 6 yr, showed that therapy with BBs was associated with a 28% increased risk of developing diabetes (HR 1.28, 95%CI 1.04–1.57), whereas therapy with thiazides, calcium channel blockers, and angiotensin converting enzyme inhibitors (ACE) carried no increase in risk of progression to diabetes *(34)*. More recently, a prospective study of 3 large cohorts examined the association of thiazides and BBs on incident diabetes *(35)*. The cohorts included 1) the Nurses' Health Study (NHS) I, including 41,193 older women (30–55 yr old); 2) NHS II, including 14,151 younger women aged 25–42 yr; and 3) the Health Professionals Follow-up Study (HPFS), including 19,472 men with a history of hypertension. After adjusting for risk factors including age, BMI, physical activity, and smoking, thiazide therapy was independently associated with increased risk of incident diabetes in all cohorts: RR 1.20 (95% CI 1.08–1.33) in older women, RR 1.45 (95% CI 1.17–1.79) in younger women, and RR 1.36 (95% CI 1.17–1.58) in men. Similarly, use of BBs independently increased the risk of diabetes among older women (RR 1.32, 95% CI 1.20–1.46) and in men (RR 1.20, 95% CI 1.05–1.38). This relationship could not be determined for younger women because the NHS II only ascertained the use of thiazides and "other" antihypertensives, a group presumably containing BBs as well as other drug classes. Therapy with ACE inhibitor or calcium channel blockers conferred a neutral risk of progression to diabetes among these cohorts.

**Table 2**
**Cardiovascular RCTs that examined incidence of new onset diabetes**

| *Trial* | *Primary treatment* | *Comparator* | *Effect of Comparator on Major CV outcomes* | *DM incidence (%) (primary/comparator)* |
|---|---|---|---|---|
| SHEP *(35)* | Placebo | Thiazide +/– BB | 34% reduction in 5 yr incidence all stroke, NF MI, CV death, all cause mortality | 3.4/2.2 |
| STOP-2 *(38)* | BB/thiazide | ACE/CCB | NS difference in CV death | NS |
| INSIGHT *(36)* | Thiazide | CCB | NS difference in composite of CV death, nonfatal stroke or MI and CHF | 7.0/5.4 |
| ALLHAT *(39)* | Thiazide | CCB or ACE | NS difference in composite of CV death or nonfatal MI | 11.6/9.8, 8.1 |
| INVEST *(37)* | BB +/– thiazide | CCB | NS difference in composite of all cause mortality, NF MI, or stroke | 8.2/7.0 |
| ASCOT *(40)* | BB +/– thiazide | CCB +/– ACE | NS difference in composite of nonfatal MI or CV death. 23% reduction in fatal or nonfatal stroke; 11% reduction in all cause mortality | 11.3/8.0 |
| CAPPP *(41)* | BB +/– thiazide | ACE | NS difference in composite of NF MI, stroke, or CV death | 7.5/6.5 |
| HOPE *(42)* | Placebo | ACE | 22% reduction in composite of CV death, MI, or stroke | 5.4/3.6 |
| CHARM *(47)* | Placebo | ARB | NS difference in all cause mortality. | 7.4/6.0 |
| VALUE *(48)* | CCB | ARB | NS difference in CV morbidity or mortality. | 16.4/13.1 |
| LIFE *(45)* | BB | ARB | 13% reduction in in CV death, MI, or stroke. | 8.0/6.0 |
| SCOPE *(46)* | Placebo | ARB | NS difference in CV death, nonfatal stroke, or nonfatal MI | NS |

Abbreviations: BB=beta-blocker, ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, CCB=calcium channel blocker, NF=nonfatal, MI=myocardial infarction, CV=cardiovascular, NS=nonstatistically significant

Data from RCTs involving BBs and thiazides, although plentiful, is somewhat difficult to interpret. The only placebo controlled trial, Systolic Hypertension in the Elderly Program (SHEP), randomized patients with hypertension to placebo versus chlorthalidone with or without atenolol *(35)*. Although SHEP demonstrated a 5% increase in diabetes incidence associated with active treatment, analysis of the primary outcome showed a 34% decrease in 5 yr occurrence of major cardiovascular events, including stroke, fatal and nonfatal MI, sudden death, and coronary artery bypass grafting. The cardiovascular benefit of thiazide +/– BB therapy outweighs the slightly increased risk of progression to diabetes.

In general, the remaining RCTs using BBs and thiazides where data is available for diabetes incidence employ these agents as control therapies. After SHEP and other trials demonstrated such a clear cardiovascular benefit of BB and thiazide therapy, withholding of active therapy became unethical, and placebo controlled trials were less frequent in the hypertension literature. Therefore, in subsequent studies, a benefit seen for the comparator (i.e., ACE, calcium channel blockers) is difficult to differentiate from a possible worsening of glycemic status owing to BB and thiazide therapy.

### *Calcium Channel Blockers (CCBs)*

The Intervention Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) was one of the earliest cardiovascular trials employing a CCB *(36)*. The study randomized 6,575 patients with hypertension (BP > 150/95) to receive the CCB nifedipine or coamilozide, a combination diuretic including hydrochlorothiazide and amiloride. The trial demonstrated no difference among the groups in the primary outcome of cardiovascular death, nonfatal stroke or MI, and CHF; however, among the 5,019 patients without diabetes at baseline, 4.3% of subjects in the CCB group developed diabetes versus 5.5 % in the co-amilozide group. A benefit from CCB versus increased risk from hydrochlorothiazide can not be determined.

Similarly, the International Verapamil-Trandolapril Study (INVEST) randomized 22,576 hypertensive patients with known coronary artery disease to a multidrug antihypertensive regimen based either on the CCB verapamil or on a non-CCB strategy using beta-blocker (BB) and thiazide diuretic therapy *(37)*. There was no difference among the treatment strategies in the primary outcome of all cause death, nonfatal MI, or stroke; however, of the 16,176 subjects without diabetes at baseline, 7.03% developed diabetes in the CCB group, compared to 8.23% in the BB/thiazide group (RR 0.85, 95% CI 0.77–0.95). Again, benefit from CCB cannot be distinguished from detriment owing to thiazide/BB therapy.

In the Swedish Trial in Old Patients with Hypertention-2 (STOP-2), 6614 hypertensive patients were randomized either to thiazide/BB, ACE, or CCB regimens *(38)*. There was no difference among the groups in cardiovascular mortality, the primary outcome. In the subgroup analysis of patients without diabetes at the study outset, (n=5893) there was a trend toward diabetes prevention in the ACE and CCB groups compared to the BB +/– diuretic group, but the trend was not statistically significant (RR 0.96, $p = 0.77$ for the ACE group; RR 0.97, $p = 0.89$ for the CCB group). This trial did not support the suspicion that BB and diuretics result in an increased incidence of diabetes.

The Anithypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was designed to compare treatment with amlodipine, lisinopril, or the thiazide diuretic, chlorthalidone *(39)*. The study randomized 33,357 hypertensive patients to base therapy on 1 of the 3 drugs, with specified stepped care to achieve a goal blood pressure <140/90. No significant difference was noted among the 3 groups for the primary composite endpoint of cardiovascular death or nonfatal MI. Among patients without diabetes at baseline ($n = 14,816$), 11.6% in the chlorthalidone group developed diabetes after 4 yr of follow up, compared to 9.8% in the amlodipine group, and 8.1% in the lisinopril group. The $p$ value for the comparison between amlodipine and chlorthalidone arms was 0.04, and the p value for comparison between the lisinopril and chlorthalidone arms was <0.001.

Most recently, the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) randomized 19,257 patients with hypertension and at least 3 other cardiovascular risk factors to a CCB based regimen (amlodipine +/– perindopril) versus a BB +/– thiazide regimen (atenolol +/– bendroflumethiazide) *(40)*. After a mean follow-up of 5.5 yr, the trial was stopped prematurely owing to excess mortality seen in the BB/thiazide group. Although the primary endpoint (nonfatal MI or cardiovascular death) did not reach statistical significance, there was a trend toward benefit in the CCB arm (HR 0.90, 95% CI 0.79–1.02). Additionally, fewer subjects in the CCB based arm had fatal or nonfatal stroke (HR 0.77, 95% CI 0.66–0.89), and all cause mortality (HR 0.89, 95% CI 0.81–0.99). Among the 19,257 subjects without diabetes at baseline, CCB based therapy was associated with a reduced incidence of progression to diabetes (HR 0.70, 95% CI 0.63–0.78). As with other studies discussed in this section, benefit of the CCB +/– ACE regimen cannot be distinguished from detriment owing to BB/thiazide.

### *ACE*

In addition to ALLHAT, STOP-2, and ASCOT, two additional trials have examined the impact of ACE on cardiovascular outcomes while providing information about diabetes incidence: the Captopril Prevention Project (CAPPP) *(41)* and the Heart Outcomes Prevention Evaluation (HOPE) *(42)*. CAPPP randomized 10,985 hypertensive patients to either captopril or BB +/– thiazide diuretic. There was no significant difference among the groups in the primary composite endpoint of fatal or nonfatal MI, stroke, and cardiovascular death. However, the captopril group demonstrated a nonsignificant trend toward reduced cardiovascular mortality compared to the BB group (RR 0.77, $p = 0.092$). In the subgroup analysis of patients without diabetes at the study outset ($n = 10,413$), 7.5% of patients in the BB group developed DM compared to 6.5% in the captopril group (RR = 0.89, $p = 0.039$).

The HOPE trial randomized 9,297 patients with or at high risk of coronary artery disease to receive either ramipril or placebo. However, the study protocol permitted the use of BB +/– thiazide in the placebo group as needed to maintain adequate blood pressure control. HOPE was stopped prematurely owing to reduced risk in the ACE group for the primary composite outcome of cardiovascular death, MI, or stroke. Randomization to ramipril was associated with reduced cardiovascular mortality (RR 0.78, 95% CI 0.70–0.86). Rates of MI, stroke, and all cause mortality were also reduced in the ramipril group. Analysis of the 5,720 patients who did not have diabetes at study outset, showed that 102 (3.6%) developed diabetes in the ramipril group, compared to 155 (5.4) in the placebo group (RR 0.66, $p < 0.001$). Although a higher proportion of individuals randomized to the

placebo group received diuretics or BB, the risk reduction of diabetes was maintained after controlling for these medications *(43)*. Therefore, subgroup analysis of diabetes incidence in the HOPE trial appears to favor ACE for diabetes prevention.

DREAM is the only ACE inhibitor trial to prospectively examine the effect on diabetes prevention *(44)*. Allocation to ramipril was not associated with a reduction in new-onset diabetes or death (HR 0.91, 95% CI 0.80 to 1.03), but was associated with a greater likelihood of regression to normoglycemia (HR 1.16; 95% CI 1.07 to 1.27, $p = 0.001$). Importantly, the trial was not powered to provide a definitive estimate of the effect of ramipril on cardiovascular outcomes, and indeed, there was no significant difference between the groups in the composite cardiovascular outcome of cardiovascular death, myocardial infarction, stroke, heart failure, angina, or revascularization. Neither DREAM nor any of the cardiovascular trials provide evidence that the use of ACE inhibitors for the express purpose of diabetes prevention is warranted.

### *Angiotensin Receptor Blockers (ARBs)*

Four cardiovascular trials using ARBs have provided inconsistent data regarding diabetes incidence: the Losartan Intervention for Endpoint reduction in hypertension study (LIFE), Study on Cognition and Prognosis in the Elderly (SCOPE) trial, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study, and the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial. LIFE randomized 9,193 patients with treated or untreated hypertension and left ventricular hypertrophy (LVH) to receive either losartan or atenolol based regimens, with goal blood pressure of < 140/90 mmHg *(45)*. After mean follow-up of 4.8 yr, the ARB based regimen demonstrated a 13 % RR reduction in the primary composite endpoint of cardiovascular morbidity and mortality, including cardiovascular death, MI, and stroke. Among the 7,998 patients without diabetes at the start of the study, 6% ($n = 241$) in the losartan group developed diabetes, compared to 8% ($n = 319$) in the atenolol group (HR 0.75, 95% CI: 0.63–0.88). Although the authors attributed the risk reduction for diabetes to modification of insulin resistance with ARB therapy, the possibility that the effect was owing to increased risk of diabetes with BB therapy could not be excluded.

SCOPE randomized 4,964 patients, 4,937 of whom were eligible for the intent to treat analysis, to candesartan versus placebo *(46)*. The trial demonstrated no difference between the 2 groups for the primary composite endpoint of cardiovascular death, nonfatal stroke and nonfatal MI. However, subjects in the candesartan group demonstrated a 27.8% reduction in nonfatal stroke and a 23.6% reduction in all stroke. No difference was seen among the groups for diabetes incidence.

CHARM randomized 7,599 patients with congestive heart failure to receive candesartan versus placebo *(47)*. After mean follow-up of 37.7 mo, there was a nonsignificant trend toward reduced all cause mortality in the ARB group (HR 0.91, 95% CI 0.83–1.00). However, the ARB group had significantly fewer cardiovascular deaths (18% for candesartan, 20% for placebo, $p = 0.012$). In the subgroup ($n = 5,439$) without diabetes at baseline, candesartan therapy was associated with significantly reduced risk of progression to diabetes. One hundred sixty three patients of 2,715 (6.0%) in the candesartan group developed diabetes, compared to 202 of 2,721 (7.4%) in the placebo group (RR 0.78, 95% CI: 0.64, 0.96, $p = 0.02$).

VALUE randomized 15,245 patients with treated or untreated hypertension and high risk of cardiovascular disease to receive a valsartan based regimen or an amlodipine based regimen *(48)*. After mean follow-up of 4.2 yr, the 2 groups did not differ significantly in the primary outcome of the study (cardiovascular morbidity and mortality). The primary outcome was seen in 10.6% of subjects in the valsartan group versus 10.4% in the amlodipine group ($p = 0.49$). Statistically significant reductions in MI (4.8% for valsartan, 4.1% for placebo, $p = 0.02$) were seen, whereas rates of CHF, stroke, and all cause mortality were similar among groups.

Among the patients without diabetes at study outset, treatment with valsartan was associated with a reduced risk of developing diabetes. Six hundred ninety (13.1%) developed diabetes in the valsartan group, compared to 845 (16.4%) in the amlodipine group ($p < 0.0001$). However, the role of thiazide therapy in this subgroup is unclear. In the trial overall, a greater proportion of patients in the valsartan group required additional medication to achieve blood pressure goals (including thiazides; use of BB and ACE was prohibited by the study protocol) compared to the amlodipine group, a relationship presumably consistent among the new diabetes subgroup.

Table 3
Levels of evidence for diabetes prevention

| *Recommendation* | *Level of evidence* |
|---|---|
| Both lifestyle interventions and metformin therapy can be safely used to delay the onset of diabetes in the short term. | 1A |
| Acarbose can delay the onset of diabetes, but its use is limited by gastrointestinal side effects | 1B |
| Troglitazone may delay the onset of diabetes, but the predominantly Hispanic female population in TRIPOD limits the generalizability of the trial results. Pioglitazone and rosiglitazone have not been studied for diabetes prevention. | 2B |
| Conflicting evidence exists to support the use of fibrates or statins for diabetes prevention. | 2A |
| No antihypertensive class has been unequivocally proven to reduce diabetes incidence. | 1B |
| BB and thiazides may increase diabetes incidence. | 2B |
| If indicated for other cardiovascular risk reduction, BB and thiazides should not be withheld from patients with IGT or metabolic syndrome. | 1B |

## CONCLUSIONS

Medical therapies inevitably entail a mixture of benefits and risks, and when they are used chronically, the balance of risks and benefits are difficult to estimate from extrapolation. Additionally, in asymptomatic conditions, adverse effects of medical therapy become less tolerable without proven benefit. Although numerous studies have demonstrated an impact of various therapeutic classes on the development of diabetes, none have been studied chronically. Consequently, whether the demonstrated reductions in diabetes incidence represent merely a delay in disease onset or true prevention remains unclear. Studies in washout populations of STOP-NIDDM and the DPP seem to indicate that treatment may have only masked underlying diabetes *(13,49)*. Additionally, none of the trials reviewed here provide any insight into the long term effect of delaying disease onset. In is unknown whether a reduction in diabetes incidence can be translated into reduced morbidity or mortality related to the disease.

In a population at increased risk of cardiovascular disease, as are patients with IGT and the metabolic syndrome, the use of antihypertensive or lipid lowering agents for diabetes prevention is particularly attractive. However, there is currently no prospective evidence that these agents can indeed reduce diabetes incidence. Additionally, none of the trials have demonstrated excess cardiovascular morbidity or mortality in the subgroup of patients developing new diabetes. Ongoing trials like NAVIGATOR, which is prospectively collecting rates of both cardiovascular events and diabetes incidence, may provide important insight into the use of antihypertensive agents in this patient population.

As such, current recommendations focus on methods proven prospectively to reduce diabetes incidence while also imposing minimal additional adverse effect (Table 3). For antihypertensive therapy, although agents not predisposing to the development of diabetes may be preferred as initial therapy, most patients will require combination therapy, thereby using medications shown to increase diabetes incidence, to achieve goals for blood pressure control. The strongest evidence for diabetes prevention by a pharmacologic agent currently is for metformin; no single agent can be recommended for diabetes prevention without more data. Future studies must be designed with sufficient follow up to evaluate the long term effects of therapy, including concomitant morbidity and mortality.

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# 7 Postprandial Hyperglycemia

*Vasudevan A. Raghavan and Alan J. Garber*

***CONTENTS***



**Summary**

In healthy individuals, blood glucose levels in the fasting state are maintained by basal insulin secretion. After a meal, the rise in postprandial glucose (PPG) is controlled by the rapid release of insulin, stimulated by both glucose and the intestinal production of incretin hormones. In diabetic individuals, postprandial insulin secretion is insufficient, resulting in postprandial hyperglycemia (PPHG). Sustained hyperglycemia results in"glucotoxicity," that results in progressively irreversible ß-cell dysfunction. There is increasing evidence that PPHG exerts a more deleterious effect on endothelial function and the vascular system, than elevation of fasting plasma glucose (FPG). In particular, individuals with normal FPG but impaired glucose tolerance (IGT) have significantly increased risk of cardiovascular events. With the recognition of the importance of PPHG and the availability of new pharmacologic options, management of diabetes will shift to greater attention to PPG levels. Currently, there are many approaches to tackle PPHG; dietary management and promotion of exercise are very effective. In particular, meglitinides, disaccharidase inhibitors, sulfonylureas and short acting insulin analogues are particularly suited to treat PPHG. The development of glucagon-like peptide 1 (GLP-1) agonists such as exendin and dipeptidyl peptidase IV (DPP-IV) inhibitors such as vildagliptin holds great promise as additional agents in achieving stringent control of PPG. There is an urgent need for the conduct of randomized controlled trials with long term follow-up, and these studies ought to be powered to study the effect of a variety of therapeutic agents that modify PPG levels, on multiple morbidity endpoints and mortality, in individuals with prediabetes, T1DM and T2 DM. Until such data is available, routine monitoring of PPG levels with a view to impact diabetic outcomes cannot be recommended.

## INTRODUCTION

### *Epidemiology of Diabetes and Prediabetes*

Abnormalities in glucose homeostasis in DM can be conveniently studied under 2 categories: 1) the fasting or postabsorptive state, which includes the 12- to 16-h following an overnight fast; and 2) the postprandial state, which is a dynamic continuum that may persist for up to 6 h after a meal is ingested. However, people usually eat at least 3 times daily and assimilation of ingested nutrients takes, on average, about 5–6 h.*(1)* The majority of the day is thus spent in the postprandial state. In nondiabetic individuals, fasting plasma glucose *(2)* concentrations (i.e., following an overnight 8- to 10-h fast) generally range from 70 to 100 mg/dL. Glucose concentrations begin to rise about 10 min after the start of a meal as a result of the absorption of dietary carbohydrates *(3)*. The postprandial glucose (PPG) profile is determined by a variety of factors: the rate and extent of carbohydrate absorption, secretory patterns of various hormones (insulin, glucagon, and incretin hormones) and their effects on hepatic and peripheral tissue glucose metabolism.

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## POSTPRANDIAL GLUCOSE REGULATION—PHYSIOLOGICAL ASPECTS

Recently, isolated postprandial hyperglycemia (PPHG), as occurs in people with impaired glucose tolerance (IGT), has been shown to double the risk for death from cardiovascular disease (CVD) *(4)*. PPHG also appears to be the rate-limiting factor for achieving optimal glycemic control in patients with T2DM *(5)*. To characterize postprandial glucose (PPG) disposal more completely, Woerle et al *(6)* used the tritiated water technique, a triple-isotope approach (intravenous [3-H(3)]glucose and [(14)C]bicarbonate, and oral [6,6-(2)H(2)]glucose), and indirect calorimetry to assess splanchnic and peripheral glucose disposal, direct and indirect glucose storage, oxidative and nonoxidative glycolysis, and the glucose entering plasma via gluconeogenesis after ingestion of a meal in volunteers, during a 6-h postprandial period. Their results suggested that in the immediate postprandial state, glycolysis accounted for approx 66% of overall disposal, with smaller contributions from glucose oxidation and storage. They found that the majority of glycogen synthesis occurred via the direct pathway from ingested glucose (approx 73%). (see Fig. 1).

Prandial regulation of glucose is a complex process. The magnitude and time of the peak plasma glucose concentration depend on a variety of factors, including the timing, quantity, and composition of the meal. In nondiabetic individuals, plasma glucose concentration peaks about 60 min after the start of a meal, rarely exceeds 140 mg/dL, and returns to preprandial levels within 2–3 h. Even though glucose concentrations have returned to preprandial levels by 3 h, absorption of the ingested carbohydrate continues for at least 5–6 h after a meal *(3)*.

Individuals with type 1 diabetes mellitus (T1DM) lack the ability to secrete insulin endogenously, and hence the time and height of peak insulin concentrations, and resultant glucose levels, tends to depend on the amount, type, and route of insulin administration. In T2DM patients, peak insulin levels are delayed and are insufficient to control PPG excursions adequately. In most diabetic individuals, abnormalities related to several processes such as insulin and glucagon secretion, hepatic glucose uptake, suppression of hepatic glucose production, and peripheral glucose uptake, all contribute to higher and more prolonged PPG excursions compared to nondiabetic individuals *(6)*. Of note, a prominent feature of T2DM is a dramatic reduction in first-phase insulin secretion (defined as the insulin normally secreted by pancreatic ß-cells within 10 min after a sudden rise in plasma glucose concentrations) *(7)*. This early insulin response appears to be lost, even in the beginning stages of the disease, when fasting glucose concentrations are only slightly elevated above normal. This defect in first-phase insulin secretion has been postulated to have the most significant impact on postprandial plasma glucose excursions, *(7,8)* and the loss of early-phase insulin release is a common defect that plays a pathogenic role in postmeal hyperglycemia.

Because the absorption of food persists for several hours after a meal in both diabetic and nondiabetic individuals, the optimal time to measure PPG concentration must be defined. A practical approach would be to measure plasma glucose 2 h after the start of a meal, as it generally approximates the peak value in patients with DM, and provides a reasonable assessment of PPHG. Specific clinical conditions, such as gestational diabetes or pregnancy in a diabetic individual may warrant glucose testing earlier (an hour following a meal) for optimal interpretation.

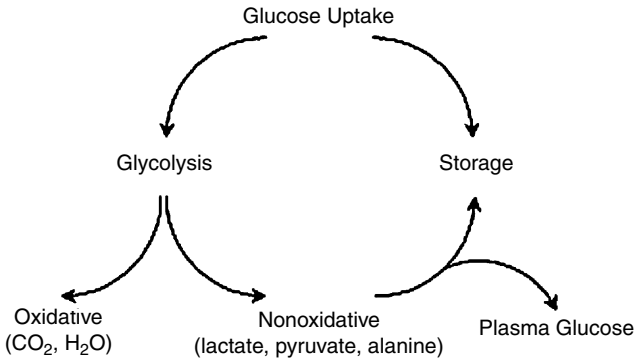


**Fig. 1.** Routes of postprandial glucose disposal.

## PATHOBIOLOGY OF HYPERGLYCEMIA

### *Glucotoxicity and Pancreatic Beta Cell Function*

Chronic hyperglycemia impairs glucose-induced pancreatic insulin secretion and insulin gene expression *(9)* through mechanisms that impact glucose desensitization, ß-cell exhaustion, and glucotoxicity. The phrase "glucose desensitization" is commonly applied to the rapid and reversible refractoriness of pancreatic ß-cell insulin exocytosis that occurs after a period of sustained exposure to hyperglycemia *(9)* and is thought of as an adaptive mechanism that occurs even when insulin secretion is inhibited, thus differentiating it from ß-cell exhaustion *(9)*. The latter phrase refers to depletion of the intracellular insulin pool available for quick release, following prolonged exposure to a secretagogue *(10,11)*. In contrast, "glucotoxicity" refers to the progressively irreversible effects of chronic hyperglycemia on ß-cell function. ß-cell secretory defects are reversible up to a point in time and become irreversible thereafter, suggesting that there is a continuum between ß-cell exhaustion and glucotoxicity, with the latter occurring more predictably after sustained hyperglycemia *(12,13)* Chronic hyperglycemia also decreases pancreatic ß-cell mass by promoting islet cell apoptosis *(14,15)*.

### *Hyperglycemia Perpetuates Hyperglycemia*

Another intriguing observation is that hyperglycemia begets hyperglycemia. Rats rendered diabetic by streptozotocin treatment or by partial pancreatectomy serve as models of fasting and postprandial hyperglycemia, with residual pancreatic beta cell function, but impaired glucose-induced insulin secretion *(16,17)*. That hyperglycemia per se may be islet cell-toxic could be inferred from the fact that the insulin secretory defect was greater than could be expected on the basis of the surviving beta cell mass. Short-term (48-h) severe hyperglycemia in normal rats impaired acute glucose-induced insulin release *(18)*. In partially pancreatectomized diabetic rats, lowering blood glucose by inducing renal glycosuria with phlorhizin (without having any direct effect on the pancreas or peripheral insulin-responsive tissues), improved both glucose-induced insulin release and insulin's effectiveness to lower glucose levels (insulin action or insulin sensitivity). This finding suggests that glucose itself may sustain the diabetogenic state *(19,20)*. It is somewhat more difficult to study glucotoxicity in humans. Osaka et al *(21)* demonstrated that lowering glycemia levels to the same extent in subjects with "maturity-onset" DM, through changes in diet, sulfonylurea, or insulin therapy resulted in the similar degrees of improvement in insulin responsiveness to oral glucose, thereby suggesting that the poor insulin response in overt DM results from both relative insensitivity of B-cells to glucose and the hyperglycemia inherent to poorly controlled DM. Glucotoxicity also induces insulin resistance that is partially reversible with improved glycemic control. Yki-Jarvinen et al *(22)* measured glucose uptake after 24 h of hyperglycemia (281 $\pm$ 16 mg/dL; using intravenous glucose) and normoglycemia (99 $\pm$ 6 mg/dL; using normal saline) in 10 patients with T1DM (age 33 $+/-$ 3 yr) treated with continuous subcutaneous insulin infusion(CSII). Insulin sensitivity (euglycemic clamp model) was significantly lower after the period of hyperglycemia than after normoglycemia. As these patients lacked endogenous insulin production, this result was thought to represent impaired insulin sensitivity owing to prior hyperglycemia.

An element of glucotoxicity could also be inferred from the association of progressive hyperglycemia with worsening T2DM. If fasting insulin and glucose concentrations are plotted in subjects with varying glucose intolerance and T2DM, an inverted U-shaped curve results (the so-called Starling curve of the pancreas) suggesting that initial compensation for hyperglycemia occurs through insulin hyper-secretion, but eventually failure of islet beta cells ensues, resulting in progressive worsening of DM *(23)*.

### *Hyperglycemia and Tissue Toxicity—Molecular Mechanisms*

Genetically determined susceptibilities have been shown for diabetic complications involving the kidneys, retina, and the heart, although specific susceptibility (allelic) variants have not yet been described. Also important are comorbidities such as hypertension (HTN) and hyperlipidemia, which tend to accelerate complications. Most tissues can protect themselves from hyperglycemia by reducing transcellular glucose transport, but many target tissues of diabetic complications, particularly vascular endothelial cells, lack this ability. Kaiser et al *(24)* exposed smooth muscle cells and endothelial cells to varying concentrations of glucose. Smooth muscle cells exposed to high glucose were able to downregulate the rate of intracellular glucose transport, but endothelial cells preincubated with high glucose could not. High intracellular glucose concentration leads to reactive oxygen

species generation and oxidative stress. Further tissue toxicity, including a proatherogenic effect could be owing to multiple mechanisms, such as activation of PKC isoforms, increased hexosamine pathway flux, increased AGE formation and/or increased polyol pathway flux *(25)* (see Fig. 2).

### *Adiposity and Tissue Effects of the Dyslipidemia—Hyperglycemia Combination—"Glucolipotoxicity"*

Altered metabolism of triglyceride-rich lipoproteins is an integral part of the atherogenic dyslipidemia in insulin resistant prediabetic individuals and T2DM patients, and is characterized typically by elevated serum triglyceride (TG) levels and decreased high-density lipoprotein cholesterol (HDL-c). Increased hepatic secretion of VLDL and decreased clearance of VLDL and intestinally derived chylomicrons result in prolonged plasma retention of these particles and accumulation of highly atherogenic partially lipolyzed cholesterol-enriched intermediate-density lipoprotein (IDL) remnants and small dense LDL particles *(26–28)*. Obesity, a major pathogenetic factor for T2DM, is characterized by increased fat cell mass, hypertriglyceridemia and excess circulating free fatty acids (FFA). Excess presence of triacylglycerols beyond the oxidative needs of lean tissue (termed "steatosis"), leads to a "spill over" effect on "lean" tissues such as liver, skeletal muscle, cardiac muscle, and endocrine pancreas., resulting in tissue dysfunction or "lipotoxicity," largely owing to potentially toxic end products of nonoxidative FFA metabolism *(29)*. This eventually leads to "lipoapoptosis" or lipid induced cell death *(30)*. This tissue-toxic effect has been attributed to the generation of specific proapoptotic lipid species or signaling molecules in response to FFA such as reactive oxygen species generation, *(31)* de novo ceramide synthesis *(32)*, nitric oxide

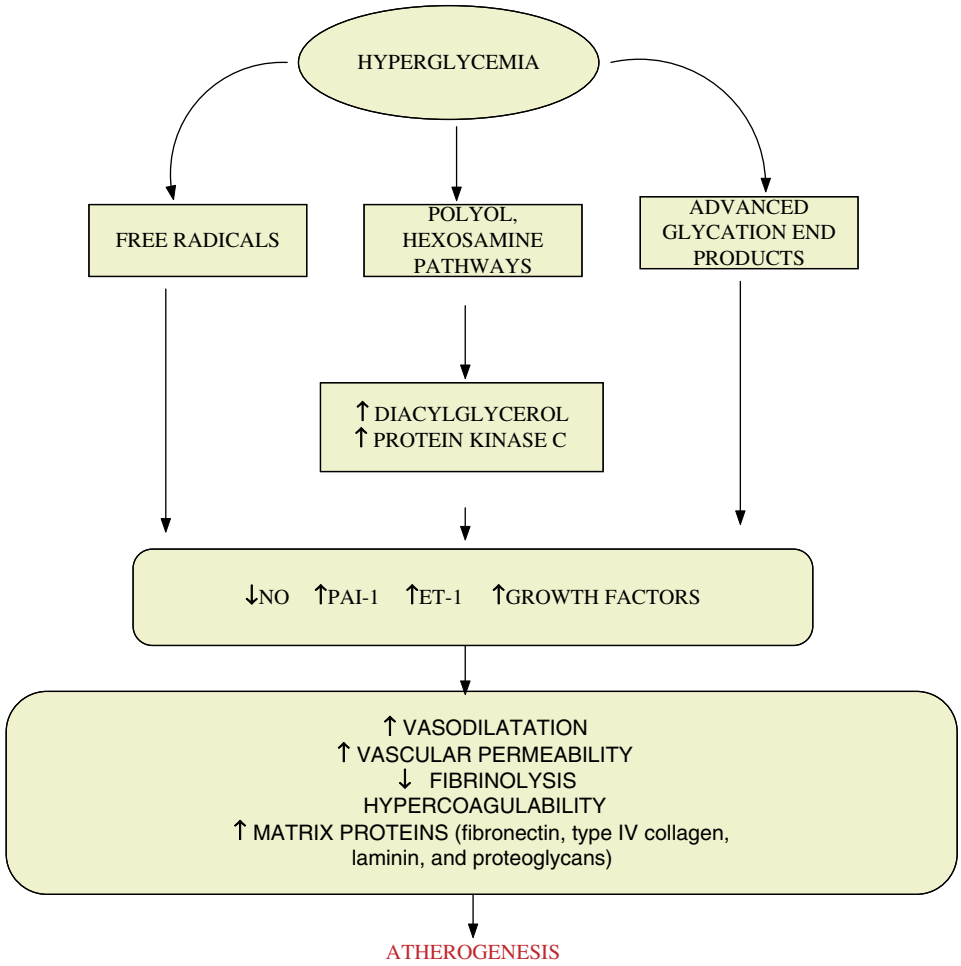


**Fig. 2.** Hyperglycemia and atherogenesis—PATHWAYS.
ET-1, endothelin-1; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1.

generation *(33)*, decreases in phosphatidylinositol-3-kinase, *(34)* and primary effects on mitochondrial structure or function *(35)*. Long chain fatty acids (LCFA's) may also suppress antiapoptotic factors such as Bcl-2 *(36)*. Similar tissue toxic effects have been described in the endocrine pancreas, and is believed to be due to products of nonoxidative metabolism of FFA such as ceramide *(37)*. More importantly, there is a growing body of evidence that suggests that FFA resulting from hydrolysis of stored triacylglycerols results in decreased glucose transport via inhibition of key glucose transporters in insulin responsive tissues such as skeletal muscle, resulting in insulin resistance *(38–40)*. Thus lipotoxicity has pancreatic (insulin secretory defects ) and peripheral (insulin resistance) effects, eventually resulting in sustained hyperglycemia.

To reconcile the roles of glucose and fatty acids in altering the function of various cell types in diabetes, in particular that of the ß-cell, Prentki et al and others proposed the "glucolipoxia" or "glucolipotoxicity" concept *(41)*. According to this model, either hyperglycemia or elevated circulating FFAs alone is perhaps not detrimental to a cell for the simple reason that when glucose levels alone are high, glucose is oxidized, and when FFAs alone are high, then they are oxidized instead of glucose. For example, FFAs are elevated during fasting, but are not toxic to cells under this low glucose condition. However, when both glucose and FFA levels are elevated in concordance, progressive tissue toxicity may ensue. Under such conditions, FFA-derived long-chain fatty acyl-CoA ester levels are high, yet they cannot be oxidized because glucose-derived malonyl-CoA is elevated as well. Malonyl-CoA regulates mitochondrial cytosolic lipid partitioning (the relative fluxes of FFA oxidation and esterification) through its inhibitory action on carnitine palmitoyltransferase-1 (CPT-1), which catalyzes the rate-limiting step leading to mitochondrial ß-oxidation of fatty acids *(42)*. As a result, FACoAs accumulate in the cytoplasm and could, for example, either directly or indirectly via complex lipid or ceramide formation cause insulin resistance in muscle tissue, impair glucose induced secretion or promote ß-cell apoptosis. This integrated model (Figure 3) of diabetes and the prediabetes in which the accumulation of acyl-CoA compounds are detrimental to various cell types, particularly at high glucose, has received support from various studies in muscle tissues *(43,44)* and ß-cells *(9)*. Recent data *(45)* suggests that postprandial hyperglycemia and postprandial hypertriglyceridemia in conjunction result in exaggerated production of cell adhesion molecules such as intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and E-selectin. These molecules are known to be elevated in DM and may be an index of endothelial activation *(46)* or even a molecular marker of early atherosclerosis*(47)*.

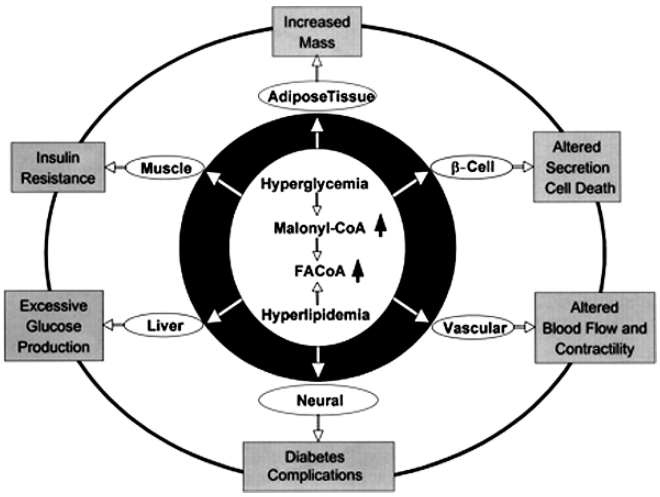


**Fig. 3.** Increased cellular levels of malonyl-CoA and fatty acyl CoA as a common mechanism causing glucolipotoxicity in various tissues in obesity-associated T2DM. Glucose-derived malonyl-CoA reduces fat oxidation, thus causing FACoA accumulation in the cytosol and consequently the exaggerated production of various reactive complex lipid-signaling molecules that may lead to pleiotropic defects in various organs. These alterations may include insulin resistance in muscle, liver, and adipose tissue; defective insulin secretion; and ß-cell death, as well as several of the complications of diabetes. Reproduced with permission from *(104)*.

## RELATIONSHIP BETWEEN FPG, PPG AND GLYCOSYLATED HEMOGLOBIN

Glycosylated hemoglobin or hemoglobin A1C ($HbA_{1c}$) is a measure of the degree to which hemoglobin is glycosylated in erythrocytes and is expressed as a percentage of total hemoglobin concentration. It reflects the exposure of erythrocytes to glucose in an irreversible and time- and concentration-dependent manner. $HbA_{1c}$ levels provide an indication of the average blood glucose concentration during the preceding 2–3 mo, incorporating both pre- and postprandial glycemia *(3)*. Blood glucose concentrations vary widely during a 24-h period and from day to day in individuals with DM and HbA1c is the most accepted indicator of long-term glycemic control. In general, FPG, PPG, and especially mean plasma glucose (MPG) concentrations, defined by the average of multiple measurements of glucose taken throughout the day, are highly correlated with HbA1c. In contrast, postprandial glucose excursions defined as the change in glucose concentration from before to after a meal, and the incremental glucose area, defined as the area under the glucose curve above the premeal (or preoral glucose tolerance test [OGTT]) value, are poorly correlated with $HbA_{1c}$. Also, HbA1c level does not provide a measure of the magnitude or frequency of short-term fluctuations of blood glucose, as happens in those with T1DM.

Although it is well established that overall glycemic control reduces diabetes related complications, the exact role of fasting and postprandial glycemia in the pathogenesis of complications in those with T2DM remains largely undetermined *(3)*. In 1997, Sauvignon et al *(48)* showed that, in those with T2DM, postlunch (2 pm) and extended postlunch plasma glucose levels (5 pm) were better predictors of glycemic control than prebreakfast values and suggested that the former indices be more widely used to supplement, or substitute for FPG in evaluating the adequacy of metabolic control in T2DM patients. More recently, Moniker et al *(49)* analyzed results of several studies reporting diurnal glycemic profiles, and found that the relative contribution of PPG was higher (70%) in patients with fairly good control of diabetes ($HbA_{1c}$ <7.3%) and decreased progressively (30%) with worsening diabetes ($HbA_{1c}$ >10.2%). In contrast, the relative contribution of FPG showed a gradual increase with increasing levels of $HbA_{1c}$. They also established that postmeal glycemia was a better predictor of good or satisfactory control of diabetes (HbA1c <7%) than was fasting glucose. The best cutoff values that ensured the optimal balance between high sensitivity and specificity (best receiver operating characteristic curve [ROC] features) were approx 200 mg/dL at 11 AM and 160 mg/dL at 2 PM. The cut-point values for predicting treatment success (specificity 90%) were 162 mg/dL at 11 AM and 126 mg/dL at 2 PM. Thus PPG seems to be a major contributor to the hyperglycemic state in most diabetic patients with "reasonable" glycemic control ($HbA_{1c} < 7$), whereas the relative contribution of FPG begins to assume a greater role in those with suboptimal/worsening metabolic status *(49)*. In contrast to the study by Monier et al *(49)*, where controlled conditions were used, El-Kebbi et al *(50)* studied 1,827 patients with T2DM and found that HbAIc was correlated with casual clinic PPG measurements taken 1 to 4 h postmeal.

## EPIDEMIOLOGIC EVIDENCE LINKING GLUCOSE LOAD AND CLINICAL OUTCOMES

Randomized controlled clinical trials, such as the DCCT *(51)* and the Stockholm Diabetes Study *(52)* in T1DM and the Kumamoto Study *(53)* and UKPDS *(2)* in T2DM have shown that therapies directed at achieving normal glycemia are effective in reducing the development and delaying the progression of long-term micro vascular complications. These and other epidemiologic studies have established a "dose-response" relationship between hyperglycemia and CVD risk. As randomized controlled clinical trial (RCT) data demonstrating reduction of CVD risk with improved glycemic control emerge, there is a growing need for setting stringent standards of care for glycemic control in those with DM.

A meta-analysis by Coutinho et al *(54)* of 95,783 people (3,707 CVD events;12.4 yr) found that the progressive relationship between elevated plasma glucose and CVD risk begins at a level well below the threshold for a diagnosis of DM. In the Norfolk cohort of the European Prospective Investigation of Cancer and Nutrition *(55)* study, hemoglobin A1C ($HbA_{1c}$ ) predicted all-cause, CVD, and ischemic heart disease (IHD) mortality continuously in men aged 45–79 yr in individuals with and without DM, and at $HbA_{1c}$ levels considered not indicative of DM. As compared with men with HbA1c <5.0%, the relative risk for CVD mortality at 4 yr was 2.53, 2.46, and 5.04 in men with HbA1c concentration of 5.0–5.4%, 5.5–6.9%, and ≥7% respectively *(55)*. In a Finnish study *(56)* with a 3.5 yr follow up, 3.4% of 1,069 nondiabetic subjects and 14.8% of 229 subjects with T2DM died from CHD or suffered a nonfatal MI. In logistic regression, T2DM was an independent risk factor for CHD.

The risk of CHD death and all CHD events in subjects with T2DM and $HbA_{1c}$ > 7.0% was significantly greater than in those with $HbA_{1c}$ < 7. (ORs 4.3 [1.1–16.7] and 2.2 [1.0–5.1]). In the Nurses Health Study *(57)* (women aged 30–55 yr), after adjusting for age, BMI, smoking, and other CVD risk factors, the relative risk for MI in diabetic women was 3.17 (95% CI 2.61–3.85) before diagnosis of T2DM and 3.97 (3.35–4.71) after diagnosis, compared with women who did not develop DM.

The UKPDS *(2)*, (3,867 newly diagnosed patients with T2DM; median follow-up 10 yr) using various regimens, found that those who received intensive therapy with sulfonylurea or insulin (mean $HbA_{1c}$ < 7.0%) had a 16% reduced risk for MI ($p = 0.052$) compared with those in the conventional group (mean $HbA_{1c}$ 7.9%), using an intention-to-treat analysis. Overall the risk in the intensive group was 12% lower (95% CI 1–21, $p = 0.029$) for any DM-related endpoint, 10% lower (−11–27, $p = 0.34$) for any DM-related death and 6% lower (−10–20, $p = 0.44$) for all-cause mortality. However, there was no reduction in the risk for macro vascular disease. A subsequent multivariable analysis of the data *(58)* ( 4,585 participants; 3,642 included in analyses of relative risk) using updated $HbA_{1c}$ levels adjusting for concomitant HTN, dyslipidemia, smoking, and age, demonstrated that hyperglycemia ($HbA_{1c}$ ) was an independent risk factor for CVD with no apparent threshold (i.e., the lower the $HbA_{1c}$ level, the lower the risk). Each 1% reduction in updated mean $HbA_{1c}$ was associated with 21% risk reduction for any DM end point (95% CI 17 −24%, $p < 0.0001$), 21% for deaths related to DM (15–27%, $p < 0.0001$), 14% for MI (8–21%, $p < 0.0001$) and 37% for microvascular complications (95% 33% −41%, $p < 0.0001$). In a substudy (UKPDS 34) *(59)*, 1,704 overweight (>120% ideal bodyweight) patients with newly diagnosed T2DM, ( mean age 53 yr; FPG 110–279 mg/dL) without hyperglycemic symptoms were randomized, after 3 mo initial diet, to either diet alone ($n = 411$; median $HbA_{1c}$ 8%) or intensive blood-glucose control policy with metformin, aiming for FPG < 110 mg/dl ($n = 342$; median HbA1c 7.4%; median follow-up 10.7 yr). A secondary analysis compared the 342 patients allocated metformin with 951 overweight patients allocated intensive blood-glucose control with chlorpropamide ($n = 265$), glibenclamide ($n = 277$), or insulin ($n = 409$). Patients allocated metformin, compared with the conventional group, had risk reductions of 32% (95% CI 13–47, $p = 0.002$) for any DM-related endpoint, 42% for DM-related death (9–63%, $p = 0.017$) and 36% for all-cause mortality (9–55%, $p = 0.011$). Among patients allocated intensive blood-glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any DM-related endpoint ($p = 0.0034$), all-cause mortality ($p = 0.021$) and stroke ($p = 0.032$).

However not all studies have corroborated the association between glycemia and CVD risk. The Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VACSinT2DM) *(60)* randomized 153 men with T2DM with suboptimal glycemic control despite maximum oral hypoglycemic agent (OHA) /insulin therapy (40–69 yr; mean follow-up 27 mo) either to standard treatment or an intensive treatment arms. New CVD event rate and CVD mortality did not differ among the groups. In regression analysis, prior CVD was the only significant predictor of new CVD events ($p = .04$). The NIDDM Patient Outcome Research Team *(61)* studied 1,539 participants (mean age 63 yr; 51% women; mean $HbA_{1c}$10.6%;mean duration of T2DM 9 yr ) undergoing usual care in a health maintenance organization; 35% took insulin and 48% took sulfonylurea. 51% had CVD and its prevalence remained constant across increasing quartiles of $HbA_{1c}$ for both genders, and was associated with the duration of T2DM (11 versus 8 yr, $p < 0.0001$). But after adjusting for established CVD risk factors, there was no association between HbA1c and CVD risk in regression analysis. The RR for any CVD event was 1.18 (95% CI 1.10–1.26), for every 1% increase in $HbA_{1c}$ *(61)*.

In The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study (22 cohorts; 29,714 individuals; 11 yr follow-up) *(62)*, men with newly diagnosed DM by the ADA fasting criteria (≥ 126 mg/dL) had a hazard ratio (HR) for death of 1.81 (95% CI 1.49–2.20) as compared to those with normal fasting glucose (<110 mg/dL); for women the HR was 1.79 (1.18–2.69). The authors suggested that fasting-glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycemia. An analysis of data from the DECODA study *(63)* (Diabetes epidemiology: collaborative analysis of diagnostic criteria in Asia study) that followed up 6,817 individuals of Japanese and Asian Indian origin between 5 and 10 yr, showed that 2-h PG was superior to FPG in predicting premature CVD related death. In a recently published metaanalysis *(64)* that included 10 studies on T2DM patients ($n = 7,435$), the pooled relative risk for CVD was 1.18, representing a 1% increase in $HbA_{1c}$ (95% CI 1.10–1.26) in persons with T2DM.

Information on the effect of glycemic control on the macrovascular complications in patients with T1DM is relatively sparse, but emerging. An early publication from the DCCT group *(65)* found a nonsignificant trend toward fewer CVD events with intensive therapy (3.2% versus. 5.4%; $p = 0.08$). The intensive insulin therapy group also had lower serum LDL-c concentrations.

In the Epidemiology of Diabetes Interventions and Complications study (EDIC) study, after 1½ yr of follow-up of the DCCT inception cohort, carotid intima-media thickness (CIMT), a measure of atherosclerosis, was similar in diabetic patients and age-matched nondiabetic controls *(66)*. However, at 6 yr, CIMT was greater in the diabetic patients than in controls and the mean progression of CIMT was significantly lesser in those who had received intensive therapy during the DCCT compared with those who had received conventional therapy; (0.032 versus 0.046 mm) *(67)* More recently, the DCCT reported the long-term incidence of CVD (1,441 T1DM patients; randomized to intensive versus. conventional therapy; mean treatment period 6.5 yr). 93% were subsequently followed until February 1, 2005 (EDIC study) and during a 17 yr mean follow-up period, 46 CVD events occurred in 31 patients in the intensive treatment arm as compared with 98 events in 52 patients who had received conventional treatment. Intensive treatment reduced the risk of any CVD event by 42% (95% CI 9–63%; $p = 0.02$) and the risk of nonfatal MI, stroke, or death from CVD by 57% (95% CI 12–79%; $p = 0.02$). $HbA_{1c}$ decrease was significantly associated with most of the positive effects of intensive treatment on CVD risk. Microalbuminuria and albuminuria were associated with a significant increase in the risk of CVD and differences among treatment groups remained significant ($p<$ or $=0.05$) after adjusting for these factors. In a recently published metaanalysis *(64)* that included 10 studies on T2DM patients ($n = 7435$), the pooled relative risk for CVD was 1.18, representing a 1% increase in $HbA_{1c}$ (95% CI 1.10 to 1.26) in persons with T2DM.

These epidemiological studies relied predominantly on measures of chronic glycemia, such as HbA1c. In the relatively few studies in which $HbA_{1c}$, FPG, and 2-h OGTT value were measured, all were similarly associated with the risk for retinopathy. The interventional studies in T1DM aimed to lower glucose levels with the goal of maintaining $HbA_{1c}$ as close to the nondiabetic range as safely possible. In the DCCT *(51)*, the primary focus of intensive therapy was to lower preprandial (up to 1 h before meals) and bedtime self-monitored blood glucose levels. If $HbA_{1c}$ goals were not achieved, further attention was focused on lowering the 90- to 120-min postprandial levels. In T2DM, the UKPDS adjusted glucose-lowering therapy to attain fasting glucose goals. Epidemiological analyses of the DCCT *(68)* and UKPDS *(58)* results reinforce the relationship among chronic glycemia, as measured by $HbA_{1c}$, and risk for developing long-term complications.

To date, there are scant clinical trial data addressing if PPG, independent of other measures of glycemia, plays a unique role in the pathogenesis of diabetes-specific complications. Similarly, outside of studies in gestational diabetes, very few studies have examined the need to treat postprandial glucose levels specifically to prevent complications. Of the several studies alluded to earlier, the Hoorn Study *(69)*, the Honolulu Heart Study *(70)*, the Chicago Heart Study *(70)* and the DECODE *(71)* (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study have clearly shown that the glucose serum level 2 h after an oral challenge with glucose is a powerful predictor of cardiovascular risk. This evidence is also confirmed by 2 important meta-analyses; The Coutinho meta analysis *(54)* and pooled data from Whitehall Study, Paris Prospective Study and Helsinki Policemen Study *(72)* involving more than 20,000 subjects. The possible role of postprandial hyperglycemia as an independent risk factor has also been supported by the Diabetes Intervention Study *(73)*, which showed that postprandial hyperglycemia predicts myocardial infarction in T2DM subjects. These studies are summarized in Table 1.

### *Postprandial Hyperglycemia—Interventional Studies and Treatment Considerations*

Although most oral antidiabetic agents and insulins lower both fasting and postprandial blood glucose levels, newer drugs are now available that specifically act to control PPHG. These drugs include alpha-glucosidase inhibitors like acarbose and miglitol, which attenuate the rate of absorption of sucrose by acting on the luminal enzymes. Adverse effects of these agents are predominantly gastrointestinal. Newer insulin secretagogues that seek to mimic the physiological release of insulin also ameliorate PPHG. These include sulfonylureas like glimepiride and nonsulfonylurea agents such as repaglinide and nateglinide. Fast-acting insulin analogs, either alone or as part of premixed formulations also help to specifically target PPHG. Finally, newer agents such as Pramlintide,

**Table 1**
**Postprandial hyperglycemia and cardiovascular mortality in clinical studies**

| *Study* | *Year published* | *Salient findings* |
|---|---|---|
| Honolulu Heart Program *(70)* | 1987 | 1-h glucose predicts coronary heart disease |
| Chicago Heart Study *(70)* | 1987 | 2-h postchallenge glucose predicts all-cause mortality |
| Diabetes Intervention Study *(73)* | 1996 | Postmeal but not fasting glucose is associated with CHD |
| Whitehall Study, Paris Prospective Study, andHelsinki Policemen Study *(72)* | 1998 | 2-h postchallenge glucose predicts all-cause and CHDmortality |
| DECODE *(105)* | 1999 | High 2-h postload blood glucose is associated with increasedrisk of death, independent of fasting glucose |
| HOORN*(65)* | 1999 | 2-h glucose better predictor of mortality than HbA1c |
| COUTINHO *(54)* | 1999 | 2-h glucose associated with CHD |
| EPIC-NORFOLK *(55)* | 2001 | HbA1c > 5% CVD mortality and HbA1c positively correlated. 0.2% reduction in HbA1c could reduce overall mortality by 10% |
| DECODA *(63)* | 2004 | 2-h PG was superior to FPG in predicting premature CVD |

an amylin analog, and glucagon-like peptide-1(GLP-1) and its analogs currently being studied hold promise in the management of patients with PPHG.

One of the earlier studies to show that targeting PPG levels has the potential to improve clinical outcome was in an obstetric setting; de Veciana et al *(74)* found that pregnant women with gestational diabetes requiring insulin therapy did better when PPG rather than FPG levels were used to guide management. The 66 women in the study were randomly assigned to either PPG (1 h after meals) or FPG monitoring to achieve a PPG of <140 mg/dL (<7.8 mmol/L) or a FPG of 60 to 105 mg/dL (3.3–5.9 mmol/L). The study found that adjusting therapy according to PPG levels resulted in a greater reduction in $HbA_{1c}$ (3.0% versus 0.6%; $p < 0.001$), lower infant birth weight (3469 versus 3848 g; $p = 0.01$), lower rates of neonatal hypoglycemia (3% versus 21%; P = 0.05) and macrosomia (12% versus 42%; $p = 0.01$), and fewer cesarean section deliveries owing to cephalopelvic disproportion (12% versus 36%; $p = 0.04$).

Ceriello et al *(75)* reported that the short acting analogue, insulin aspart, reduced postprandial oxidative stress more effectively than did regular insulin. The study involved 23 patients with T2DM and 15 normal matched controls. For the patients with type 2 diabetes, a standard meal was preceded with regular insulin (0.15 unit/kg body weight); for matched controls, a standard meal was preceded with insulin as part (0.15 unit/kg body weight). Oxidative stress in the arteries was assessed by measuring nitro-tyrosine at the start of the meal and 1, 2, 4, and 6 h afterwards. The study found that nitro-tyrosine levels were significantly elevated in people with diabetes versus control subjects ($p < 0.001$) and that they became further elevated post prandially. Insulin aspart was significantly more effective than regular insulin at reducing both PPG levels ($p < 0.04$) and postmeal nitro tyrosine levels. ($p < 0.03$). Postprandial TG levels were unchanged by insulin aspart versus regular insulin in the study, indicating that the reduction in oxidative stress was unlikely to be a result of lowering TG. In a follow-up study with a similar design published 2 yr later *(76)* insulin aspart significantly improved endothelial function compared with regular insulin, thereby suggesting that oxidative stress and endothelial dysfunction are closely inter-related. Twenty-three patients with type 2 diabetes and 10 normal controls again were given a standard test meal; however, in this study, the meal was preceded by 0.15 unit/kg body weight of regular insulin for controls and 0.15 unit/kg body weight insulin aspart for diabetes patients. Flow mediated vasodilatation in the brachial artery was measured by blinded examiners using ultrasound at intervals after the meal. Meals had no effect on flow mediated vasodilatation in the control subjects, although there was a significant decrease in the diabetes patients ($p < 0.001$). Insulin aspart significantly improved arterial function compared with regular insulin ($p < 0.01$). As in the previous study,

TG levels were similar in the 2 groups, implying that, by lowering postprandial hyperglycemia, insulin aspart had a beneficial effect on the vascular endothelium.

Beisswenger et al *(77)*, using a double-blind crossover design, studied 21 T1DM subjects who were administered either insulin lispro or regular insulin. They found a highly significant correlation between PPG excursions and postprandial excursions in plasma levels of 2 highly reactive precursors of advanced glycation end products (AGEs): methylglyoxal (MG) and 3-deoxyglucosone (3-DG) levels. Levels of these compounds were not correlated with $HbA_{1c}$ ($r = 0.01$; $p = 0.95$), supporting the notion that the formation of these compounds were a direct consequence of acute hyperglycemia, not chronic hyperglycemia.

The results of another double-blind, randomized, placebo controlled study *(78)* found that regulating PPG levels with acarbose reduced nuclear factor kappa B (NF-kB) activation after 8 wk of treatment in 20 T2DM patients ($p = 0.045$). NF-kB mediates the expression of a host of atherosclerotic mediators, including cytokines, adhesion molecules, clotting factors, endothelin-1, and the receptor for AGEs

In a seminal study organized by the Campanian Postprandial Hyperglycemia Study Group *(79)*, 175 drug-naive patients with T2DM (93 men and 82 women; 35–70 yr of age) were randomized to either repaglinide ($n = 88$) or to glyburide ($n = 87$), with a 6–8 wk titration and a 12-mo treatment phase. Carotid intima media thickness (CIMT) was compared by using blinded serial assessments of the far wall. After 12 mo, decrease in HbA1c was similar in both groups but repaglinide was more effective in blunting the postprandial glucose peak (148+/-28 mg/dL versus. 180+/-32 mg/dL respectively; $p < 0.01$) (Figure 4). CIMT regression, defined as a decrease of >0.02 mm, was observed in 52% of diabetics receiving repaglinide and in 18% of those receiving glyburide ($p < 0.01$). Interleukin-6 ($p = 0.04$) and C-reactive protein ($p = 0.02$) decreased more in the repaglinide group than in the glyburide group. The reduction in CIMT was associated with changes in postprandial but not fasting hyperglycemia, and those who had the greatest reduction in postprandial hyperglycemia had the greatest CIMT regression ($r = 0.21$; $p = 0.01$). The results could not be explained by differences in classical CV risk factors such as body mass index, lipids, and blood pressure. In a metaanalysis *(80)* that included data from 7 randomized, double blind, placebo-controlled, long-term studies of acarbose in T2DM patients, data from patients treated with either acarbose ($n = 1248$) or placebo ($n = 932$) for at least 1 yr were pooled to obtain the primary outcome of time to first CV event. Most patients also were taking a concomitant medication, either a sulfonylurea (31% in the acarbose group versus 38% in the placebo group), metformin (4% versus 5%), or insulin (11% versus 12%). The study found that patients taking acarbose remained event-flee significantly longer than patients on placebo ($p = 0.006$). Pooled data showed that 9.4% of the placebo group experienced a CV event versus 6.1% of the acarbose group, a significant 35% reduction in relative risk (RR) ($p = 0.006$). There was also a 64% reduction in RR of a myocardial infarction (0.72% versus 2.04%; $p = 0.012$). As the majority of patients (56.5%)

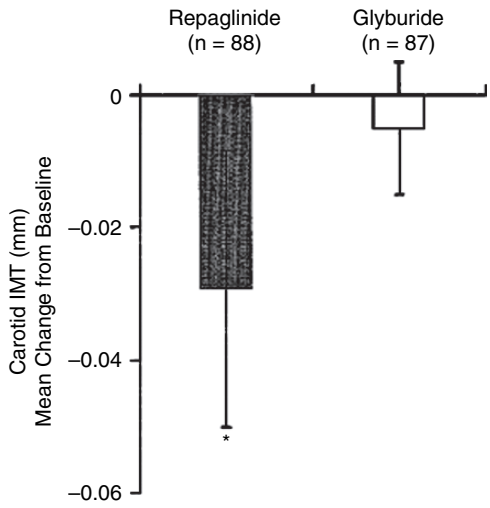


**Fig. 4.** Regression of atherosclerosis after 12 mo of therapy: Repaglinide produced a more significant regression of mean carotidintima-media thickness (IMT) than glyburide *$p = 0.02$. Data from *(79)*.

were on concomitant cardiovascular medications, it was thought that acarbose had an independent additive cardio-protective effect, possibly attributable to better control of PPG. In a Japanese study *(81)*, 30 obese T2DM subjects were randomly assigned and treated for 3 wk, with either diet alone or diet plus voglibose (0.9 mg daily) ($n$ = 15 each). Analysis of the diurnal metabolic profiles revealed a significant reduction of postprandial hyperglycemia and hyperlipidemia in the voglibose group relative to the control group ($p < 0.05$), despite similar improvement in body mass index and hemoglobin HbA1c in both groups. Voglibose also significantly decreased plasma levels of soluble intercellular adhesion molecule 1 and urinary excretion of 8-iso-prostaglandin F2 alpha and 8-hydroxydeoxyguanosine ($p < 0.01$) and C-reactive protein ($p < 0.05$) relative to the control group.

In another small study *(82)* that was designed to compare the efficacy of 3 insulinotropic agents in each admission, placebo or study medications were administered before 3 isocaloric meals as follows: immediate-release glipizide 30 min before breakfast and 30 min before supper, glipizide gastrointestinal therapeutic system (GITS) 30 min before breakfast, or nateglinide 120 mg 10 min before breakfast, before lunch, and before supper. Blood was drawn for analysis of glucose, insulin, and C-peptide at –0.05, 0, 0.25, 0.5, 1, 2, 3, and 4 h relative to each test meal. Once-daily glipizide GITS, twice-daily immediate-release glipizide, or thrice daily administration of nateglinide resulted in equivalent control of postmeal hyperglycemia inT2DM.

The STOP-NIDDM trial *(83)* an international double-blind, placebo-controlled, randomized trial involving 1,429 patients with IGT, found a 49% RR reduction for any CV event in patients treated with acarbose over a mean follow-up of 3.3 yr (2.2% versus 4.7%; $p$ = 0.03). A single-center, ultrasound substudy *(84)* over the same period involving 132 of the 1429 STOP-NIDDM participants found that acarbose 100 mg TID significantly reduced the progression of carotid IMT relative to placebo ($p < 0.05$). Patients on acarbose had an annual mean IMT progression rate similar to those previously reported for comparable healthy subjects, which was half the rate of patients taking placebo. Over a mean 3.3-yr follow-up, IMT increased by 0.05 mm in the placebo group versus only 0.02 mm in the acarbose group ($p$ = 0.027) *(84)*.

Several small studies have looked at the efficacy of using regimens containing rapid acting insulin analogs to control PPG excursions. Feinglos et al *(85)* using an open label randomized crossover design, studied 25 T2DM subjects who were poorly controlled on maximal doses of sulfonylureas. In one arm of the study, patients continued therapy with maximum-dose sulfonylureas. In the other arm, patients used a combination therapy with insulin lispro before meals and sulfonylureas. After 4 mo, Insulin lispro + sulfonylurea therapy significantly reduced 2-h postprandial glucose concentrations compared with sulfonylureas alone, from 335 mg/dL to 256 mg/dL] ($p < 0.0001$) along with a statistically significant decrease in the incremental postprandial glucose levels ($p < 0.0007$). FPG levels were decreased from 10.9 to 8.5 mmol/l ($p < 0.0001$), and HbA1c values were reduced from 9.0 to 7.1% ($p < 0.0001$). Total cholesterol was significantly decreased in the lispro arm from 5.44 to 5.10 mmol/l ($p < 0.02$). HDL cholesterol concentrations were increased in the lispro arm from 0.88 to 0.96 mmol/L ($p < 0.01$). Bastyr et al *(86)* randomized 135 T2DM patients to one of three interventions, all of which included glyburide (G): insulin lispro (L+G); premeal blood glucose with metformin (M+G); bedtime NPH insulin (NPH+G). At 3 mo, $HbA_{1c}$ was significantly lower with all therapies ($p$ = 0.001) and was significantly lower for L+G (7.68+/–0.88%) compared with either NPH+G (8.51+/–1.38%, $p$ = 0.003) or M+G (8.31+/–1.31%, $p$ = 0.025). Fasting blood glucose (FBG) at end point was significantly lower for NPH+G (153 ± 47 mg/dL) compared with either L+G (190 ± 35 mg/dL, $p$ = 0.001) or M+G (174 ± 52 mg/dL, $p$ = 0.029). The mean 2-h postprandial blood glucose after a test meal was significantly lower for L+G (196 ± 52 mg/dL) versus NPH+G (220 ± 56 mg/dL, $p$ = 0.052) or versus M+G (229 ± 59 mg/dL, $p$ = 0.009). In another double blind study *(87)* 20 T2DM subjects (10 female, 10 male; mean BMI 31; mean $HbA_{1c}$ 7.4) were admitted overnight on 4 occasions and prescribed, in random order, 10 mg glipizide (30 min premeal), 120 mg nateglinide (15 min premeal), 10 mg glipizide plus nateglinide (30 and 15 min premeal, respectively) or placebo pills (30 15 min premeal). Blood was drawn for analysis of glucose, insulin, and C-peptide at -0.05, 0, 0.5, 1, 2, 3, and 4 h relative to the meal. Peak and integrated glucose excursions did not differ significantly between glipizide and nateglinide. However, by 4 h postmeal, plasma glucose levels were significantly higher with nateglinide (9 +/– 0.9 mmol/L) compared with the premeal baseline (7.8 +/– 0.6 mmol/L, $p$ = 0.04) and compared with the 4-h postprandial glucose level after administration of glipizide (7.6 +/– 0.6 mmol/L, $p$ = 0.02). Integrated postprandial insulin levels were higher with glipizide (1,556 +/– 349 pmol/h. l) than nateglinide (1,364 +/– 231 pmol/h. l; P = 0.03). Early insulin secretion, as measured by insulin levels at 30 min postmeal, did not differ between glipizide and nateglinide.

The mammalian incretin hormone glucagon-like peptide (GLP)-1 augments first-phase insulin secretion in healthy subjects *(88,89)*, subjects with impaired glucose tolerance *(90)*, and patients with T2DM *(89,91)*. Exenatide is a 39-amino acid peptide incretin mimetic that exhibits gluco-regulatory activities similar to those of GLP-1 *(92)*. These actions include glucose-dependent enhancement of insulin secretion *(93,94)*, suppression of inappropriately high glucagon secretion and slowing of gastric emptying *(94,95)*. Exenatide's glucose-dependent enhancement of insulin secretion may be mediated by its binding to the pancreatic GLP-1 receptor *(96)*. However, exenatide has a prolonged half-life after subcutaneous injection of 2–3 h, as compared to that of GLP-1 which is approx 20 min *(95,97)*. An additional benefit is that exenatide treatment is often accompanied by weight loss *(98,99)*. Early data suggest that short-term exposure to exenatide can restore the insulin secretory pattern in response to acute rises in glucose concentrations in T2DM patients who, in the absence of exenatide, do not display a first phase of insulin secretion. A 30-week, double-blind, placebo-controlled study *(100)* was performed in 733 subjects (aged 55 ± 10 yr, BMI 33.6 ± 5.7 kg/m*(2)*, $HbA_{1c}$ 8.5 ± 1.0%; means ± SD) all of whom had type 2 diabetes and were unable to achieve adequate glycemic control with maximally effective doses of combined metformin-sulfonylurea therapy. They were randomized to twice daily (BID) 5 μg subcutaneous injections of exenatide (arms A and B) or placebo (saline) for 4 wk, in addition to therapy with metformin and a sulfonylyurea drug. Thereafter, one arm remained at the same dose, whereas in the other arm, the dose was increased to 10 μg BID. Exenatide-treated DM2 subjects had an insulin secretory pattern similar to healthy subjects in both first (0–10 min) and second (10–180 min) phases after glucose challenge, in contrast to saline-treated DM2 subjects.

Yet another related class of agents are the dipeptidyl peptidase IV (DPP IV) inhibitors. Two agents, Vildagliptin and Sitagliptin, are currently being evaluated in clinical trials, for which some outcomes data are available. These agents act by inhibiting DPP IV, an enzyme that cleaves GLP-1, prolonging its half-life. In a recent study *(101)*, 279 patients with T2DM went through a 4-wk run-in placebo phase and a 12-wk active treatment phase in which they received vildagliptin (25 mg twice daily, 25, 50, or 100 mg once daily[qd], or placebo). There was a statistically significant reduction in $HbA_1c$ levels in the vildagliptin 50 mg qd ($p = 0.003$) and 100 mg qd groups ($p = 0.004$) compared with the placebo group. The mean 4-h PPG level was significantly reduced from placebo in the vildagliptin 50 mg qd group ($p = 0.012$) and mean 4-h postprandial insulin was significantly increased from baseline versus. placebo in the vildagliptin 100 mg qd group ($p = 0.022$). β-cell function assessed by HOMA-B was significantly increased in the vildagliptin 100 mg qd treatment group ($p = 0.007$). The incidence of adverse events was similar in all treatment groups including placebo.

## CONCLUSION

Achievement of near perfect glycemic control remains elusive for most diabetic patients for a variety of reasons and, as discussed earlier, CVD continues to be a leading cause of death in these individuals. A review of the data on PPG and CV risk suggests that postprandial hyperglycemia may be the missing link. However, there is a paucity of clinical trial data addressing whether PPG, independent of other measures of glycemia, plays a unique role in the pathogenesis of CVD and other diabetes-specific complications. Interventional studies have not demonstrated a convincing beneficial effect of glucose lowering on CVD (macrovascular) outcomes *(2,51)* and thus far, no clinical trials have examined whether treatments that primarily lower PPG decrease cardiovascular events. Associations of CVD and CVD risk factors with glycemia have been demonstrated over a broad range of glucose tolerance, from normal to diabetic, in several epidemiological studies. Whether the FPG or a post challenge (OGTT) glucose level is an independent risk factor for CVD in these studies is controversial at present and warrants more studies. At present, HbA1c measurements remain the "gold standard" for assessing long-term glycemic control. As to whether measuring premeal glucose, FPG or PPG, either alone or in combination, is helpful in adjusting treatment to achieve HbA1c goals while minimizing hypoglycemia remains largely unanswered. It is also unclear whether excessive excursions of PPG have a significant impact on the development of diabetic microvascular and macrovascular complications independent of HbA1c levels. To address this fundamental question, outcome studies must be designed to control FPG versus PPG levels while aiming to achieve similar and acceptable HbA1c levels *(102)*.

In the absence of concrete randomized controlled clinical trial data, it is somewhat difficult to recommend routine PPG monitoring as part of the overall treatment plan in those with T1DM and T2DM. However, the

following are clinical situations, summarized in Table 3, in which PPG monitoring may be worthwhile *(102)*. See Table 2 for grades of recommendations.

a) Suspected postprandial hyperglycemia. In patients who achieve their premeal glucose targets, but whose overall glycemic control as determined by $HbA_{1c}$ is inappropriately high, PPG monitoring and therapy to minimize PPGEs may be beneficial. [1c]
b) Monitoring treatment aimed at specifically lowering PPG. In patients with T1DM or T2DM who are treated with glucose lowering agents expected primarily to reduce PPG, monitoring may be useful in titrating these treatments or in confirming that patients have in fact responded to the intervention. It is also possible that PPG monitoring may be beneficial to evaluate the effect of changes in nutrition or exercise patterns. [1c]
c) Hypoglycemia. Hypoglycemia in the postprandial period is rare except in response to exercise or rapid-acting insulin analogs.

Are there agents that are superior in terms of controlling PPG? α-glucosidase inhibitors [1b], rapid acting oral insulin secretagogues [1b], and rapid-acting insulin analogs [1b] are the classes that predominantly lower PPG. They also reduce HbA1c. It is unclear, however, as to the extent of contribution of PPG lowering (versus FPG lowering) to mean reductions in $HbA_{1c}$. Furthermore, it is not clear whether therapies that target PPG provide unique benefits relative to other pharmacological therapies that lower HbA1c comparably; performing such studies will be important.

There is an urgent need for the conduct of randomized controlled trials with long term follow-up, and these studies ought to be powered to study the effect of a variety of therapeutic agents that modify PPG levels, on multiple morbidity endpoints and mortality, in individuals with prediabetes, T1DM and T2DM. One such study

**Table 2**
**Grades of recommendations**

| *Grade of recommendation* | *Clarity of risk/benefit* | *Methodologic strength of supporting evidence* | *Implications* |
|---|---|---|---|
| 1A | clear | Randomized trials data without important limitations | Strong recommendation;can apply to most patients in most circumstances without reservation |
| 1B | clear | Randomized trials with important limitations | Strong recommendation; likely to apply to most patients |
| 1C+ | clear | No randomized trials for this specific patient population, but results from RCT including different patients can be unequivocally extrapolated to the patient under current consideration; or overwhelming evidence from observational studies is available | Strong recommendation; can apply to most patients in most circumstances |
| 1C | clear | Observational studies | Intermediate-strength recommendation; may change when stronger evidence is available |
| 2A | unclear | Randomized trials without important limitations | Intermediate-strength recommendation. Best action may differ depending on circumstances or patients' or societal values |
| 2B | unclear | Randomized trials with important limitations | Weak recommendation; alternative approaches likely to be better for some patients under some circumstances |
| 2C | unclear | Observational studies | Very weak recommendation; other alternatives may be equally reasonale. |

Table 3
Recommendations

| *Recommendation* | *Level of evidence* |
|---|---|
| Monitoring PPG in those with near normal FPG and suboptimal HbA1c | 1C |
| Reduction of postprandial hyperglycemia in type 2 diabetic patients is associated with CIMT regression | 1C |
| Use of alpha glucosidase inhibitors in individuals with pronounced postprandial hyperglycemia | 1B |
| Use of prandial insulin therapy [insulin lispro, insulin aspart] either alone or in combination with basal insulin therapy to treat postprandial hyperglycemia | 1B |
| Use of meglinitide agents in those with postprandial hyperglycemia and suboptimal HbA1c | 1C+ |

currently underway is the "Hyperglycemia and its effect after acute myocardial infarction on cardiovascular outcomes in patients with Type 2 diabetes mellitus (HEART2D)" Study *(103)*. This multicenter study with a projected follow up of 3 yr will enroll approx 1,355 T2DM patients using infarct severity and peri-infarct treatment as randomization factors. Patients will be assigned to 1 of 2 insulin treatment strategies: 1) postprandial strategy: premeal insulin lispro with basal insulin at bedtime if needed (NPH insulin), targeting 2-h PPBG < or = 7.5 mmol/L (135 mg/dL)or 2) basal strategy: insulin (NPH insulin twice daily or insulin glargine once daily; or premixed human insulin (70% NPH/30% regular] twice daily), targeting fasting and premeal blood glucose (BG$\leq$ 6.7 mmol/l or 120 mg/dL). Both groups will aim for a target HbA1c < 7%. It is anticipated that a difference in PPG (2-2.5 mmol/l or 30–35 mg/dL) among strategies will yield at least a 15–18.5% relative risk reduction in CV events for the postprandial strategy, but this remains to be seen.

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# 8 Medical Nutrition Therapy in Type 2 Diabetes

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***CONTENTS***



**Summary**

Medical Nutrition Therapy is a cornerstone of diabetes management. While its effectiveness to reduce A1C by 1–2% has been demonstrated when delivered by registered dietitians, all members of the medical care team need to understand the basic elements of MNT to reinforce the care plan. Although an integral part of the treatment strategy, patients with type 2 diabetes are particularly challenged by the need for weight loss. However, there are other strategies besides a calorie-restricted diet that will improve metabolic measures. Patients and providers alike may be confused by the myriad messages related to level of carbohydrate recommended, glycemic index, fiber and the diet-of-the-day in the popular press. This chapter, divided in three sections, includes 1) an overview of popular messages, separating fact from fiction, 2) a summary of the evidence based nutrition recommendations for each nutrient and 3) guidelines for weight reduction.

**Key Words:** Nutrition; carbohydrate; meal planning; weight management; diet; dietitian; glycemic index; type 2 diabetes.

## INTRODUCTION

Medical Nutrition Therapy (MNT) is commonly described as the "cornerstone" of diabetes treatment. It is an integral component of diabetes prevention, management, and self-management education. This is particularly true for type 2 diabetes. As reported in the American Diabetes Association Standards of Medical Care, "People with pre-diabetes or diabetes should receive individualized MNT as needed to achieve treatment goals, preferably provided by a registered dietitian familiar with the components of MNT" *(1)*.

The effectiveness of MNT is well documented. Randomized controlled nutrition therapy outcomes studies have documented decreases of A1C of 1% in newly diagnosed type 1 diabetes, 2% in newly diagnosed type 2 diabetes and 1% in type 2 diabetes with an average duration of four years *(2)*. In addition, the effectiveness of MNT in the prevention of type 2 diabetes was demonstrated in the Diabetes Prevention Program, in which there was a 58% relative risk reduction in the progression to diabetes with intensive lifestyle modification (modest weight loss and increased physical activity) *(3)*.

However, it is frequently acknowledged that patients find following a diet the most challenging part of the diabetes regimen. Also, physicians are often poorly trained in nutrition and do not have the time to provide patients with an individualized meal plan. In a diabetes education needs assessment survey, 107 primary care physicians and 521 clinical office staff reported that, of *six* diabetes topics, nutrition and exercise are taught *least* well to patients. In addition, only 28% reported frequently referring patients to a diabetes educator *(4)*. In another study evaluating physician's confidence in their knowledge and effectiveness regarding counseling in risk

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reduction behaviors, 36% of 255 physicians responding felt knowledgeable about weight management techniques compared to 3% who were confident they succeeded in their practice. Similarly, 36% felt confident in nutrition knowledge, while only 8% felt they succeeded in their practice *(5)*.

Thus, not only does a gap exist between provider knowledge and perceived effectiveness of nutrition related behaviors, the ever increasing economic and time constraints in a busy physician practice limit what is realistic to accomplish in a brief office visit. Despite good intentions, patients may be handed a preprinted diet tear-off sheet and told "watch what you eat," or "lose some weight." This advice inevitably results in poor compliance and "diet failure." At the same time, the patient may be coming to the physician with a list of questions regarding the latest diet fad or newspaper article on some new connection between diet and health, looking for answers. Therefore, given the importance of MNT, the delivery of evidence-based information can enhance the effectiveness of therapy and correct nutrition misinformation.

This chapter is divided into three main sections. The first addresses five practical guidelines for physicians related to enhancing nutrition care. It offers a variety of resources and guidelines to assist the physician in providing patients with realistic nutrition recommendations. The second section includes specific information related to developing and implementing a nutrition prescription. This is particularly helpful for providers who many not have easy access to a registered dietitian. Finally, the third section briefly addresses options to consider for MNT for overweight and obese patients with type 2 diabetes.

## RECOMMENDATIONS TO ENHANCE NUTRITION CARE

Ideally, every physician should have access to a registered dietitian familiar with the components of diabetes MNT and an education program recognized by the American Diabetes Association for providing quality self-management training services. Unfortunately, this is impossible. Since behavior change is complex, and weight management is a chronic condition that should be addressed at every visit, we propose five recommendations to assist the healthcare provider in the more effective incorporation of nutrition care into the therapy of patients with type 2 diabetes: 1) adopt a collaborative approach, 2) dispel nutrition myths and provide facts, 3) assess lifestyle first, then develop prescription, 4) set realistic goals and 5) identify reliable resources.

### Adopt a Collaborative Approach

Much attention has been given to the Chronic Care Model and its place in diabetes self-management. According to this model, optimal chronic care is achieved when a prepared, proactive practice team interacts with an informed, activated patient *(6)*. The model features a patient-professional partnership, involving collaborative care and self-management education. Diabetes nutrition care fits perfectly into this model. In order to maximize effectiveness, the lifestyle changes should be mutually determined between patient and provider. The focus of education is on problem-solving and real-world application instead of a more traditional didactic approach *(7)*. By adopting a more collaborative approach, the patient and provider will agree on dietary changes that are realistic and achievable. Taking it one step further and asking the patient to describe implementation intentions (such as what will be done, how and when) can further increase the likelihood of behavioral change *(8)*.

### Dispel Nutrition Myths and Provide Facts

The media has flooded the American public with messages about diets, food, and nutrition. Most of us get confused by the myriad number of messages, and it becomes difficult to assist patients in sorting through fact from fiction. To add to the confusion, many nutrition messages that have been given to patients for years rely more on tradition than on science. Only recently have organizations such as the American Diabetes Association critically looked at the recommendations to ensure that they are truly evidence based. The following nutrition myths are the most common:.

**Myth 1: A diabetic diet for women is 1,200 calories and for men is 1,400 calories:** There is no such thing as "a diabetic diet." There is no set way to define and prescribe a meal plan for persons with diabetes. It is important to recognize that each prescription and plan will be unique based on individual eating patterns and metabolic needs. Preprinted diet sheets that were common as handouts for many years are inappropriate. They do not take into account the differing preferences, cultural eating styles, and medical needs unique to each patient.

Because there are so many ways to develop a meal plan, it is important to identify which are the most important metabolic priorities and to focus the nutrition recommendations to meet those priorities. For example, if the priority is glucose control, an initial MNT plan that focuses on carbohydrate control and meal timing consistency may be the most important message. If the priority is weight loss, overall calorie reduction and an increase in energy expenditure will be the emphasis. If hyperlipidemia is being addressed, a reduction in saturated and trans fats will be the priority. For some patients, a meal plan higher in carbohydrate may be appropriate, while others, whose triglycerides or glucose control is exacerbated by excess carbohydrate, may limit carbohydrate consumption to 40% of total calories.

**Myth 2: Avoid sugar and anything that is white:** Scientific evidence does not support the long held belief that sucrose and sugar be restricted for glycemic control. The former view of looking at carbohydrates as "complex" or slower-acting and "simple" or fast-acting is not useful or accurate. Numerous studies have demonstrated that equivalent carbohydrate amounts of sugars and starches produce similar responses in glycemia *(9)*. Although there are many reasons why sugar should be limited in the diet, it is misleading to blame sugar as the culprit for hyperglycemia, when all carbohydrates raise blood glucose.

Likewise, generalizations such as "stay away from anything that is white," or "avoid all fruit juices" can convey confusing messages to patients. Certainly, whole grain products such as whole wheat breads, brown rice, and whole grain cereals are richer in fiber and nutrients than their refined counterparts, but it does not mean the "white" version can not be eaten. In many cases the glycemic impact differences between white and whole grain products is very minimal. Patients are commonly told they can not have fruit juice. However, a message regarding control of the portion size is more important to convey.

**Myth 3: A low glycemic index diet is recommended for anyone with diabetes:** The glycemic index (GI) has received considerable attention in recent years. This is a system of classifying carbohydrate foods according to their impact on blood glucose. Foods with the highest GI have the most impact on glycemia. For ease of application, foods are classified into high (GI >70), medium (GI 55–70) and low (GI <55) and patients are urged to choose more foods from the low GI lists. Examples of foods in the high list include: white bread, plain bagel, baked potatoes, watermelon, cooked carrots, and refined cereals (such as cornflakes). Low GI foods include rye bread, steel cut oatmeal, nuts, lentils, yogurt, apples, and bananas *(10)*.

Rating a food only on the GI is somewhat misleading and does not address the whole constellation of factors that can affect the glycemic effect of a food. For example, knowing the total amount of carbohydrate ingested is of highest importance. Based on only GI information, many individuals are avoiding otherwise healthy foods like carrots because they fear the glycemic consequences that may result. Thus, a more useful measurement has been developed called glycemic load (GL) that takes into account both the GI and the amount of carbohydrate in a single serving of a food. The GL is determined by multiplying the GI of a food by the grams of carbohydrate in a serving divided by 100. (GI × grams of carbohydrate /100) Thus, although carrots have a high glycemic index [92], there are only 8 gms carbohydrate in a usual serving (1/2 cup); thus, the overall GL [7] is low. Patients can be assured that a reasonable serving of carrots will have a minimal effect on blood glucose. In contrast, while a chocolate and caramel cookie bar has a low GI [44], the amount of carbohydrates in a serving is high [40], yielding a GL of 17, more than twice that of carrots. Other factors that may affect how a food alters blood glucose include the ripeness of the food, physical form, degree of cooking and processing, as well as the individual's blood glucose level.

A meta-analysis reviewing 14 studies revealed that low GI diets reduced HbA1C by 0.43% compared to high GI diets. The authors suggest that this small but clinically significant effect supports the choice of more low GI foods. *(11)* However, more recent studies have called into question the utility of GI and GL. A study that examined food questionnaires from more than 1,000 people over five years found no significant correlation between the GI of the foods consumed and the blood glucose levels of participants *(12)*.

The GI remains controversial, and research on the GI will undoubtedly continue. In the mean time, healthcare providers are encouraged to consider possible effects of higher GI foods when "fine-tuning" glycemic control. Pre- and postmeal blood glucose values can be used to assess the impact of particular meals and to determine if glycemic control can be improved by changing one or more of the higher GI foods to a lower GI alternate

(e.g., substituting steel cut oats for instant oatmeal or cornflakes, or replacing potatoes with barley). However, an individualized MNT plan delivered by a registered dietitian can reduce A1C by 1–2%, significantly more than what might be expected from a low GI diet.

**Myth 4: A low-carbohydrate diet is best for losing weight:** Some version of a low-carbohydrate diet likely has been tried by most people attempting weight loss in recent years. Whether known as Atkins, South Beach, or any of the other variations, meal plans that strictly limit carbohydrate (usually less than 30 g/d) have been the most popular of the "fad" diets.

Despite its popularity, research demonstrating the effectiveness of low carbohydrate diets has been limited, and long term efficacy has not been shown. A systematic review of 107 studies of low carbohydrate diets concluded that weight loss was associated with restriction of calorie intake but not with reduced carbohydrate content *(13)*. Very few studies in this review were longer than 90 days duration. Another group assessed the effects of a low carbohydrate diet of one year's duration and found that, although weight loss was more significant in the study group than in the control group at 3–6 months, by the end of the year both groups had about the same amount of weight loss *(14)*. Finally, four different popular diet approaches were compared in a one-year randomized trial. The authors concluded that each diet modestly reduced body weight and several cardiac risk factors, with no advantage seen in the low carbohydrate diet. It should also be noted that overall adherence rates were low *(15)*.

The key issue is overall calorie reduction, not whether the diet is low-fat or low-carbohydrate. While some patients may find initial success by greatly reducing or omitting carbohydrate foods, low-carbohydrate intake is not a long term solution. In addition, glucose is the primary fuel for the brain and the central nervous system; thus, restricting carbohydrate to less than 130 g/d is not recommended except for short term periods (upto one year) *(1)*.

Contrary to earlier, more dismal statistics, recent data demonstrate an increase in the number of people successfully maintaining weight loss. In a study of 500 adults, 228 of whom were overweight or obese, 20% had intentionally lost at least 10% of their body weight and maintained the loss for at least a year *(16)*. Lessons learned from the National Weight Control Registry indicate that those successful in maintaining long term weight loss share several common characteristics. These include engaging in high levels of physical activity on a regular basis (approx 1 h /d), eating a low calorie, lower fat diet, eating breakfast regularly, self-monitoring weight and maintaining a consistent eating pattern across weekdays and weekends *(17,18)*.

**Myth 5: Carbohydrate counting is only for type 1 diabetes:** In the 1990s, the DCCT brought attention to carbohydrate counting for patients with type 1 diabetes. However, this is by no means a new approach to the nutrition management of diabetes. In 1935 Elliott Joslin wrote, "In teaching patients their diet, I lay emphasis first on the carbohydrate values, and teach to a few only the values for protein and fat." Carbohydrate counting is not an exclusive tool for type 1 diabetes. It can also be very useful in type 2 diabetes. The provider can help the patient identify sources of carbohydrate and appropriate portion sizes, and make food choices that foster consistent carbohydrate intake. Food lists emphasizing portion control of 4 carbohydrate food groups (milk, fruit, starches and sweets/desserts) teach patients the serving sizes of foods in 15-g carbohydrate portions. Initial education emphasizes recognition of these 15 g reference serving sizes, followed by label reading for more precise carbohydrate values. Table 1 can be used to establish an initial meal plan for patients with type 2 diabetes. Frequent blood glucose monitoring before and after meals can help patients "fine tune" their food choices at meals and snacks.

**Table 1**
**Carbohydrate guidelines for each meal for patients with type 2 diabetes**

| | |
|---|---|
| If you are male and not overweight | 4–5 carb servings (60–75 gms) |
| If you are female and not overweight | 3–4 carb servings (45–60 gms) |
| If you are overweight (>10 lbs) | Subtract 1 carb serving (15 gms) |
| If you exercise aerobically 3–5 times a week | Add 1 carb serving (15 gms) |
| Snacks: If desired or needed, 1–2 carb servings (15–30 gms) | |

A patient on basal-bolus insulin regimens or using an insulin pump can use carbohydrate counting as a carbohydrate-to-insulin ratio to determine pre-meal insulin doses. A correction or sensitivity factor can also be calculated to correct high blood glucoses. Before initiating this type of insulin therapy, it is important that the healthcare provider work with the dietitian to assess the patient's carbohydrate counting skills, as accuracy is essential to determine the bolus insulin dose. The carbohydrate ratio can be calculated by dividing 450 by the total daily dose of insulin used by the patient. For example, a patient using 30 units of insulin per day would have a carbohydrate:insulin ratio of 15:1 or 1 unit of insulin for every 15 grams of carbohydrate eaten. The correction factor can be calculated by dividing 1,500 by the total daily dose. The same patient using 30 units of insulin per day would have a correction factor of 50 (1 unit of insulin to lower the blood glucose 50 mg/dL). It is important that patients using carbohydrate ratios and correction factors monitor their blood glucose frequently.

### Assess Lifestyle First, Then Determine Prescriptions

Incorporating collaborative care principles, the therapeutic plan should be constructed around patients' usual habits and their readiness to change. For example, to determine an appropriate insulin regimen, the patient's usual eating and activity patterns should be evaluated first. It is much easier to design a medication plan around typical lifestyle behaviors than it is to change lifestyle behaviors, which can be difficult, to match an insulin regimen.

In general, small, achievable, patient-initiated changes can make a substantial difference in treatment success. Table 2 offers suggestions for assessing particular nutrition-related problem areas. Small changes in the timing

**Table 2**
**Tips for Conducting a Nutrition Assessment *(51)***

| *Nutrition habits to evaluate* | *Ask* | *Rationale* |
|---|---|---|
| Relations between food intake and home blood glucose results. | "Have you noticed any trends between what you eat and your blood sugar results?" | • Determine if there is a pattern connecting food intake and glucose results. Target recommendations to address the problem; for example, do not skip breakfast if prelunch hypoglycemia has been occurring. |
| Usual eating and exercise habits-in terms of timing, quantity and consistency. | "What times are your meals and snacks eater? Does that vary much from day to day? Describe two different typical lunches you might have." | • The medical prescription should be based on a patient's usual lifestyle habits, and not the other way around. Sometimes dramatic improvements in glucose control can be realized if emphasis is placed on the important of eating, consistent amounts at consistent times. |
| Sources of fat in the diet. | "How do you prepare meats? Vegetables? What kind of fried foods do you eat regularly? What type of milk or cheese do you use? How often do you eat baked goods, desserts (sources of hidden fats)?" | • Help patient identify specific foods that contain fat that can be limited or substituted for a lower-fat choice. Avoid general recommendations, such as "limit fried foods," but contract with the patient for a specific action to take. |
| Frequency of eating away from home. | "How many times each week do you eat a meal away from home?" | • Frequent fast-food and restaurant meals can contribute a significant source of fat and calories. Help the patient identify ways to improve eating habits when on the go. |
| Past nutrition education and efforts to follow a diet. | "Tell me about any of the diets you have received in the past. What worked and what did not?" | • Determine not only if the patient has received proper nutrition instruction, but also what experience, both positive and negative, they have with diets. |

*(Continued)*

Table 2
*(Continued)*

| *Nutrition habits to evaluate* | *Ask* | *Rationale* |
|---|---|---|
| Use of vitamin and mineral supplements and botanical and herbal products. | "Tell me about any supplements that you take, such as vitamins." | • A study showed that up to 33% adults practice some sort of alternative medicine, but few tell their physicians. It is important to encourage the patient to feel comfortable describing such practices. |
| Persons responsible for food purchasing and preparation. | "Who does the shopping and cooking at home?" | • Whenever possible, nutrition education should include the person who obtains and prepares the food. Because food affects the whole family, the more the family is involved and understands, the better the compliance. |
| Overall nutritional balance. | "Tell me everything you ate over the past 24 hours." | • A quick assessment of an adult's overall nutritional health should pay particular attention to the following: intake of 4–6 servings of fruit or vegetables; 2–3 servings of milk, yogurt or sources of calcium; food choices low in saturated fat and high in fiber; moderate portion size of meat, fish, and poultry (generally not more than 6-8 oz/day); only moderate use of sodium, cholesterol, alcohol, and added sugars. |
| Frequency of skipping or missing an insulin dose. | "How many times a week might you forget to take your insulin?" | • Asking in nonjudgmental, nonthreatening way may foster honest dialogue about skipped insulin doses that may, in fact, be intentional. Women in particular recognize lipogenic properties of insulin and learn that skipping it can be a quick way to lose weight. This unhealthy route to weight control must be addressed. |
| Readiness to change (related to a particular behavior). | "Is starting a weight loss program something you are ready to do now? Within the next 3 months? Maybe sometime later?" | • For a patient to adopt a new behavior, they must be ready to take action, you can still help him or her progress along the stages of change and move from just thinking about it to preparing to take action. |

of meals, maintaining consistency in the amount of carbohydrate eaten, or substituting low glycemic index foods for higher ones, can have a significant impact on metabolic control. When referral to a registered dietitian is not possible, and time is limited, the assessment should focus on one or two of these important areas, rather than telling the patient to "cut back on the calories" or to follow a diet sheet. For example, the healthcare provider can guide the patient in the identification of several sources of carbohydrate that may adversely affect blood glucose and have him or her suggest action steps (such as substituting a lower carbohydrate alternative, cutting down portions or omitting altogether). Note, however, that the nutritional priorities for the person taking insulin will be different from those of the person not taking insulin.

### Set Realistic Goals

In order to assess the effectiveness of MNT, regular monitoring of laboratory values such as HbA1C, fasting plasma glucose (FPG), lipids, weight, and blood pressure is essential. However, in order to see measurable

change from MNT, the patient must be given time to incorporate the new eating habits into his or her lifestyle. Before moving the patient from diet as a monotherapy to diet and oral agents, the patient requires at least 6–8 wk to implement recommended dietary changes. The patient and the healthcare provider should have realistic expectations. For example, MNT can only be expected to reduce HbA1C in type 2 diabetes from 1–2% *(19)*. It can, however, have beneficial impact on a variety of other parameters, including reduction of LDL and blood pressure (Table 3). If goals are not met, given an adequate trial, advance the therapy to the next level by adding or adjusting medication. This does not indicate the "failure" of the diet or of the patient; rather, it is consistent with the natural history of diabetes and/or the failure of the provider to develop the right recommendations and set realistic, collaborative goals with the patient.

### Identify Reliable Resources

A registered dietitian (RD) is the first resource to identify, as every patient with diabetes should have the benefit of receiving an individualized meal plan and ongoing follow-up. Carefully researched nutrition practice guidelines guide the nutrition care process followed by the RD to ensure consistency and quality of care *(20)*. Recently, MNT for diabetes and renal disease became recognized by Medicare as a reimbursable service. Up to 3 h of counseling during the first calendar year and two hours in each subsequent year is eligible for reimbursement. In order for the services to be reimbursed, there must be a written referral by a physician (not a nurse practitioner or physician's assistant), and the patient must have documented diabetes (not pre-diabetes or metabolic syndrome) *(21,22)*.

When possible, the provider should work collaboratively with the dietitian, discussing therapeutic goals and expectations of treatment interventions. The written referral should include the therapeutic goals (target HbA1C, FPG), relevant laboratory data (HbA1C, lipids, BP, renal function tests), list of medications and other medical problems. If available, certified diabetes educator (CDE) dietitians can serve expanded roles beyond providing nutritional therapy, including providing training in blood glucose monitoring and interpretation, calculating carbohydrate-to-insulin ratios, as well as insulin adjustment and risk factor reduction guidelines. Excellent web-based resources can link the provider to a registered dietitian or diabetes educator in a specified geographic area *(23,24)*.

If a qualified dietitian is not an option, other resources may be available within the community, especially to provide support for weight control. Programs such as Weight Watchers or Jenny Craig may be excellent choices

**Table 3**
**Effect of MNT on Lipids and Blood Pressure *(33,34)***

| | *Approximate LDL Reduction** | *Approximate Systolic BP Reduction*** |
|---|---|---|
| Weight Reduction | | |
| • Reduce 10 lbs | 5–8% | |
| • Reduce 22 lbs | | 5–20 mm Hg |
| Saturated Fat; <7% of calories | 8–10% | |
| Dietary cholesterol; <200 mg/day | 3–5% | |
| Viscous fiber; 5–10 gm/day | 3–5% | |
| Sterols/stanols; 2 gm/day | 6–15% | |
| Dietary sodium; 2400 mg/day | | 2–8 mm Hg |
| Adopt DASH eating plan; rich in fruits, vegetables, low fat dairy; reduced fat | | 8–14 mm Hg |
| Physical activity; 30 min/day, most days | | 4–9 mm Hg |
| Moderate Alcohol consumption; no more than 1 drink (men) – 2 drinks (women) per day | | 2–4 mm Hg |

DASH – Dietary Approaches to Stop Hypertension
*Adapted from (ref 33)
**Adapted from (ref 34)

Table 4
Resources and Publications for Nutrition Education

Several organizations and diabetes centers publish material for diabetes nutrition education. (Accessed February 13, 2006)
- American Diabetes Association
  www.diabetes.org
- American Dietetic Association
  www.eatright.org
- Diabetes Education Program
  www.ndep.nih.gov
- Foreign Language Nutrition Materials (in addition to Spanish)
  http://monarch.gsu.edu/multiculturalhealth
  http://www.metrokc.gov/health/reach/diabetes.htm
- Joslin Diabetes Center
  www.joslin.org
- International Diabetes Center
  www.idcpublishing.com
- WIN Weight control information network.
  http://win.niddk.nih.gov/publications/tools.htm
- National Kidney Foundation
  http://www.kidney.org

for patients who would benefit from structure and ongoing motivation. Early evidence suggests a benefit from web-based, interactive nutrition websites for weight control *(25)*.

Several organizations have published nutrition guidelines and algorithms to assist the physician in providing comprehensive care for patients with type 2 diabetes. Both the Texas Diabetes Council and the Joslin Diabetes Center have web-based guidelines that may be printed as a handy reference *(26,27)*. In addition, there are a variety of free resources for patient nutrition education (Table 4).

## PROVIDING NUTRITIONAL GUIDANCE FOR YOUR PATIENTS

The goal of MNT is to prevent and treat the chronic complications of diabetes by attaining and maintaining optimal metabolic outcomes, including blood glucose and HbA1C levels, LDL and HDL cholesterol and triglyceride levels, blood pressure and body weight. Although having access to a registered dietitian who is experienced in diabetes management is ideal, the primary care provider will lay the basic groundwork. The provider needs to be able to develop and implement a basic nutrition prescription, and give guidance and recommendations related to the use of food and alcohol to achieve these metabolic goals. The following section offers basic tools to complete these tasks.

### *Developing the Nutrition Prescription*

A question frequently asked of dietitians is "how long does it take to teach a diet?" There is no simple answer. Because patients have a wide variety of backgrounds and experiences, the teaching time can vary greatly. In addition, MNT is not as straightforward as providing a piece of paper with eating instructions on it. It is recommended that a four-step-nutrition care process be followed to ensure behavior change that will result in modified eating habits *(28)*. The four steps include assessment, goal setting, implementation, and evaluation. In general, the dietitian will schedule a new patient assessment for one hour, followed by at least one to two 30-minute follow-up sessions within the first month. This is necessary to assess the effectiveness of the therapy. After a trial period of at least 6–12 weeks, if the metabolic goals are not met, MNT should be advanced *(29)*.

Medical nutrition therapy must be based on evidenced-based recommendations. However, the best available evidence must still be moderated by individual circumstance and preferences. While an understanding of the guidelines is essential, the provider must also recognize that for some patients, the recommended "diet" might be to simply guide the patient to reduce or omit high carbohydrate foods, such as sugar-sweetened soft drinks,

and decrease portion sizes. The following section summarizes the recommendations for MNT and the evidence that supports these recommendations.

### Calories

Weight reduction is recommended for all overweight (BMI 25.0–29.9 kg/m$^2$) or obese (BMI $\geq$ 30 kg/m$^2$) adults thereby reducing the risk of developing type 2 diabetes. The weight reduction goal should be achievable and maintainable. Moderate weight reduction of 5% body weight can produce significant health benefits. A calorie deficit of 500–1,000 kcal/d from usual calorie intake can result in a 1–2 pounds/wk weight reduction *(30)*. An alternate approach for estimating energy intake to achieve weight reduction is based on the individual's body weight (Table 5).

The distribution of calories recommended for healthy adults is 45–65% of total calories from carbohydrate, 20–35% from fat and 10–35% from protein. Individualized meal plans should be based on patient food preferences, meal times, diabetes medications, and metabolic goals. An individual with elevated low-density lipoprotein (LDL) cholesterol may need to keep fat intake at 20–25% of total calories, whereas an individual with elevated triglycerides may need to reduce carbohydrate intake to 40–45% of total calories *(1)*.

### Carbohydrate

The American Diabetes Association, in agreement with the National Academy of Sciences – Food and Nutrition Board, recommends a range of carbohydrate between 45–65% of total calories *(1)*. However, others suggest that slightly lower amounts of carbohydrate (approximately 40% total calories) might be particularly beneficial for weight reduction and hyperglycemia management *(31,32)*.

The amount and type of carbohydrate in foods influences blood glucose levels; therefore, all carbohydrate consumption should be controlled. Patients need to learn which foods contain carbohydrate and to eat consistent, controlled amounts at meals and snacks. Table 6 shows a variety of carbohydrate foods in differing portion sizes that all contain 15 g of total carbohydrate. It is noteworthy that the serving size of the sweeter or sugary foods is smaller than their less sweet counterparts, reflecting the higher carbohydrate content. Patients should be cautioned that carbohydrate counting alone can lead to unwanted weight gain and an increased fat intake if they are not conscious of the hidden fats in their diets.

**Fiber:** A healthy diet should include generous quantities of high-fiber, unprocessed foods (whole grains, legumes, fruits and vegetables). General guidelines suggest the consumption of 20–35 g of dietary fiber daily from a wide variety of foods (or 14 g fiber per 1,000 kcal). There is little convincing evidence, however, that dietary intake of 25–30 grams of fiber has specific glycemic benefits, although there does appear to be a relationship between increased soluble fiber (from oats, barley and legumes) and a reduction in serum lipids *(33)*. A study of very high fiber intake (50 g/d) did demonstrate a reduction in serum lipids, improved glycemic control and decreased hyperinsulinemia *(35)*. However, a fiber intake of 50 grams/day is not realistic for most patients. As Table 7 illustrates, the fiber content of even "high" fiber foods does not contribute significant amounts of fiber per serving.

**Table 5**
**Alternative approach for estimating energy intake goal of initial weight loss diet *(30)***

| *Body weight (lbs)* | *Suggested goals for energy intake (kcal/day)** |
|---|---|
| 150–199 | 1000–1200 |
| 200–249 | 1200–1500 |
| 250–299 | 1500–1800 |
| 300–349 | 1800–2000 |
| >350 | 2000 |

*The energy intake goals in this table would achieve an energy deficit that is slightly greater than the 500–1000 kcal deficit recommended for moderate weight loss, allowing for potential errors in estimating the caloric value of foods consumed.

Table 6
Carbohydrate Choices: 15 g carbohydrate serving sizes

| | |
|---|---|
| Starches, breads, cereals, vegetables | Fruit |
| • Rice, pasta–1/3 cup cooked | • Apple or orange–1 small |
| • Bread–1 oz / 1 slice | • Raisins–2 Tbsp |
| • Oatmeal–½ cup cooked | • Apple or orange juice–½ cup |
| • Unsweetened dry cereal –¾ cup | • Cranberry or prune juice–1/3 cup |
| • Sweetened cereal–1/3 cup | |
| Milk | Desserts and Sweets |
| • Fat free, 1%, 2%, whole milk-1 cup | • Regular ice cream-1/2 cup |
| • Plain yogurt-1 cup | • Regular cookie-1 oz. |
| | • Jam, jelly or syrup-1 Tbsp. |

**Nonnutritive Sweeteners:** There are now 5 different types of non-nutritive or artificial sweeteners on the market; saccharin, aspartame, acesulfame K, sucralose, and neotame. All are U.S. Food and Drug Administration (FDA) approved, have undergone rigorous scrutiny and have been shown to be safe when consumed by the public, including people with diabetes and women who are pregnant *(1)*. In 2001, saccharin was removed from the list of potential carcinogens; however, because it crosses the placenta and may remain in fetal tissue due to slow fetal clearance, some groups continue to recommend limiting saccharin during pregnancy *(36)*.

**Nutritive Sweeteners:** Reduced calorie sweeteners approved by the FDA include sugar alcohols (mannitol, sorbitol, xylitol, hydrogenated starch hydrolisates), and tagatose. Sugar alcohols produce a lower postprandial glucose response than sucrose or glucose and have a lower calorie content. Sugar alcohols, on average, contain approximately 2 calories per gram, compared to other sugars that provide about 4 calories per gram. Thus, when counting carbohydrates one should subtract one-half of sugar-alcohol grams from total carbohydrate to obtain a more accurate estimate of impact carbohydrates.

### Dietary Fats

Patients with diabetes are considered to be at similar risk for cardiovascular events as individuals without diabetes who have had a prior event. Therefore, the goal for dietary fat intake is the same for the two groups. The National Cholesterol Education Program (NCEP) dietary guidelines recommend a total fat intake of 25–35% of calories, total cholesterol intake less than 200 mg/d, and saturated fat intake <7% of total calories *(33)*. Trans

Table 7
Sources of Dietary Fiber

| | | Approx gms fiber per svg |
|---|---|---|
| Whole Grains | Whole grain bread-1 oz. slice | 2 |
| | Brown rice-1 cup | 3 |
| Fruit | 1 medium piece | 3 |
| Vegetables | ½ cup cooked; 1 cup raw | 2 |
| Dried Beans | Lentils (1/2 cup) | 4 |
| | Black bean soup (1/2 cup) | 5 |
| | Dried beans, cooked (1/2 cup) | 7 |
| Brans and supplements | Wheat bran (2 Tbsp) | 3.2 |
| | Oat bran (2 Tbsp) | 1.6 |
| | Psyllium seed husks (2 Tbsp) | 8 |
| | Flax seeds (3 Tbsp) | 7 |
| | Metamucil (1 dose) | 3.4 |
| Nuts | Almonds (1 oz) | 4 |
| | Walnuts (1 oz) , | 1.5 |

Adapted from The Doctor's Pocket Calorie, Fat & Carbohydrate Counter *(50)*.

fat intake should also be limited because both saturated fat and trans fat are the primary dietary influences on plasma LDL cholesterol. Trans fat is found in processed foods containing partially hydrogenated vegetable oils and in oils used to prepare fried foods in most restaurants and fast food chains. A total fat intake of cholesterol raising fatty acids (saturated and trans fat) should not exceed 10% of total calories *(37)*.

Dietary interventions that aid in reducing LDL cholesterol are encouraged. These interventions include the reduction of saturated fat and dietary cholesterol intake, the inclusion of unsaturated fats, viscous fiber, plant stanols and sterols, and reduction of body weight. The estimated cumulative LDL reduction is 20–30%, as illustrated in Table 4. The NCEP recommendation for polyunsaturated fat is up to 10% of total calories, and monounsaturated fat up to 20% of total calories. Sources of polyunsaturated fat include corn oil, safflower oil, soybean oil, and nuts and seeds. Monounsaturated fats can be found in olives and olive oil, peanuts and peanut oil, avocado, canola oil, and fish.

Omega 3 fat intake, particularly EPA and DHA omega fats, have been shown to be effective in reducing serum triglycerides and for the prevention of primary and secondary heart disease. It is generally recommended that persons eat at least 2 fatty fish servings per week for the prevention of primary heart disease and 1 fatty fish serving per week for secondary prevention *(9,36)*. Alternatively a fish oil supplement can be used that contains EPA and DHA. Food sources of omega 3 fats include fatty fish (tuna, salmon, and mackerel), flaxseed and flaxseed oil, canola oil, soybean oil, and nuts. The fish sources of omega 3 fats appear to be more beneficial than the plant sources. Fish oil supplements can enhance the effect of blood thinners and should be used cautiously *(37)*.

### Protein

With adequate insulin, protein has very little effect on blood glucose levels. The dietary reference intake (DRI) acceptable macronutrient distribution range for protein is 10–35% of energy intake and the recommended dietary allowance ( RDA) is 0.8 g high quality protein/kg body weight/day. *(1)* However, dietary intake of protein in individuals with diabetes is similar to that of the general population and usually does not exceed 20% of energy intake. The effect of increasing protein intake to 30% of calories recently has been studied. Dietary protein stimulates insulin secretion in type 2 diabetes and thus there may be a glycemic advantage to increasing protein levels *(38)*. If this percentage is prescribed, lean sources of protein such as non-fat dairy products, fish, skinless poultry, lean meats, and vegetable proteins should be utilized.

Particular dietary protein sources may be of benefit to individuals with type 2 diabetes. Soy proteins containing soy isoflavones have been shown to reduce serum cholesterol and LDL cholesterol in hypercholesterolemic patients. In October 1999 the FDA approved a health claim of reduced risk of heart disease on the label of foods that contain more than 6.25 g of soy protein per serving, assuming an intake of four servings per day, giving a daily total of 25 g soy protein. However, a recent study of 55 postmenopausal women did not show a beneficial effect of soy protein on serum lipids *(39)*.

Slowing the progression of kidney disease is one of the primary goals of diabetes treatment. Proven interventions that slow the progression of kidney disease include strict glycemic control, strict blood pressure control, and angiotensin-converting enzyme inhibition or angio-tensin-2 receptor blockade. There is also evidence that even small reductions in dietary protein from usual amounts (0.8 g/kg body weight or slightly lower for people with clinical nephropathy) will retard the progression of renal disease *(9)*.

### Alcohol

Because alcohol is not metabolized to glucose and inhibits gluconeogenesis, it may have a hypoglycemic effect within 6-36 hours after ingestion. Therefore, if patients choose to drink alcoholic beverages, they should drink with meals and not on an empty stomach. In addition, self-monitoring of blood glucose before and after alcohol intake enables the patient to predict potential hypoglycemia and to prevent it. If there are no other contraindications to alcohol intake (such as pregnancy, hypertriglyceridemia, pancreatitis, or risk for abuse) one drink per day for adult women and less than two drinks per day for adult men is generally considered acceptable *(1)*. Alcohol does contribute significant calories and should be limited for weight control. If combined with carbohydrate containing mixers, such as fruit juices or sodas, the carbohydrate content must be counted.

There is accumulating evidence to support benefits from the ingestion of moderate amounts of alcohol, including decreased risk of type 2 diabetes, coronary heart disease, and stroke *(9)*. Interestingly, the cardio-protective effects

of alcohol are not determined by the type of alcoholic beverage. Although some studies show slight benefits for wine drinkers, this may be due to advantageous lifestyle characteristics (lower rates of smoking and obesity.) *(40)*. While light to moderate alcohol consumption does not raise blood pressure, there is a strong association between chronic, excessive intake and elevated blood pressure *(9)*.

### Vitamins, Minerals, and Supplements

Because nearly one-third of American adults take some type of nutritional supplement, it is important for providers to assess intake in an open, nonjudgmental way. Patients must be made to feel comfortable disclosing information about supplements. A multi-vitamin/mineral supplement is generally recommended for adults attempting weight reduction, the elderly, pregnant or lactating women, and strict vegetarians *(9)*.

There are controversies regarding the use of chromium supplementation in diabetes to improve glucose tolerance, weight loss and glycemia. Although some studies have demonstrated a benefit of supplementation *(41)*, this research has been criticized for numerous flaws, and other, well-designed studies have not demonstrated a significant benefit *(42)*. Although there may be some value in chromium replacement in deficiency states, chromium deficiency is difficult to identify. A recent FDA statement concluded there is insufficient evidence to support any of the proposed health claims, and a meta-analysis of randomized controlled trials also found no benefit of chromium picolinate supplementation in reducing body weight *(43)*. The RDA for adults is 20–25 micrograms for women and 30–35 micrograms for men. Dietary sources of chromium include meats, coffee, tea, whole wheat, and rye flours, and brewer's yeast.

The category of supplements known as antioxidants has received considerable attention. These include vitamin E, vitamin C, and beta-carotene. Observational studies have shown a correlation between antioxidant consumption and prevention of disease states. However, large placebo-controlled clinical trials have shown no benefit and in some cases have suggested adverse effects *(1,44)*.

Finally, there is limited scientific evidence on the effectiveness of complimentary and alternative medicine (CAM) for type 2 diabetes. However, because CAM continues to increase in popularity, physicians must assess patient use and belief in such approaches. In a study conducted by the National Center for Complementary and Alternative Medicine, 62% of adults in the US are using some form of CAM, including prayer, multi-vitamin therapy, and acupuncture *(45)*. Some of the more common herbal or botanical products used by persons with diabetes include alpha-lipoic acid (claimed to help insulin sensitivity, neuropathy and weight loss), coenzyme Q 10 (claimed to reduce heart disease risk), and garlic. Nopal (cactus) has been used in traditional Mexican medicine to treat diabetes. Uncontrolled studies have demonstrated a glucose lowering effect. It is thought this effect may be due to the fiber content of cactus. High risk or toxic herbal supplements include bitter melon (in the rind and seeds), goat's rue, and bilberry. Use of these supplements is not recommended. Supplements are regulated by the FDA as foods rather than drugs. As a result, there could be quality issues in the manufacturing process. In addition, supplements can interact with prescribed or over-the-counter medications and other supplements.

## NUTRITIONAL MANAGEMENT OF OVERWEIGHT AND OBESE PATIENTS

The prevalence of overweight and obesity is becoming epidemic. More than two thirds of adults are considered overweight or obese, including 80–90% of the patients with type 2 diabetes. Type 2 diabetes in children and adolescents is increasing in parallel with the rise in childhood obesity. It is easy to focus on the crisis of overconsumption of food, inactivity, and dismal success statistics and conclude that successful weight loss may be a losing battle.

However, as demonstrated by numerous studies, including the UKPDS and the Diabetes Prevention Program, a modest reduction in weight of only 5–10% can yield significant results *(30)*. Weight loss may have the most impact on glycemic control if it occurs early in the disease process. In addition, energy restriction is at least as important as, if not more important than, weight loss for glycemic control.

Data from the National Weight Control Registry is also encouraging. Approximately 20% of individuals are successful at long term weight loss when defined as the loss of 10% of initial body weight, with maintenance of the loss for at least one year *(17)*. In addition, 83% of registry participants reported a trigger for their weight loss, with the most common trigger being medical in nature (such as a diagnosis of diabetes). Thus, providers should discuss the benefits of even modest weight reduction as soon as possible with patients with newly diagnosed diabetes.

**Table 8**
**Guide to Selecting Treatment *(47)***

| | *BMI category (kg/m$^{2)}$* | | | | |
|---|---|---|---|---|---|
| Treatment | 25–26.9 | 27–29.9 | 30–34.9 | 35–39.9 | >40 |
| MNT, physical activity and behavioral therapy | With co-morbidity | + | + | + | + |
| Pharmacotherapy | | With co-morbidity | + | + | + |
| Surgery | | | | With co-morbidity | + |

The Practical Guide: Identification, Evaluation and Treatment of Overweight and Obesity in Adults. Washington DC: US Department of HHS; 2000. NIH Publication No.02-4084. http://www.nhlbi.nih.gov/guidelines/obesity/practgde.htm

In addition to MNT, pharmacotherapy or surgery may be considered as the BMI increases (Table 8) *(47)*. In addition to consideration of medication for weight reduction, the patient's diabetes medications should be carefully evaluated to determine whether different options should be considered to facilitate weight loss. (Table 9) For example, exenatide, despite being administered by injection, has been well received initially by patients with type 2 diabetes, largely due to its side effects of weight loss.

**Table 9**
**Nutrition Implications of Diabetes Medications *(46)***

| *Diabetes Treatment* | *Medication* | *Nutrition and Weight Management Considerations* |
|---|---|---|
| Sulfonylureas Second generation | Glyburide (Glynase®, Micronase®, DiaBeta®) Glipizide (Glucotrol®/Glucotrol XL®Glimepiride (Amaryl®) | • Increased risk for hypoglycemia; Could potentially increase eating for hypoglycemia treatment or prevention (starting with lowest daily dose and gradually increasing will minimize risk)<br>• Increased risk for weight gain, probably secondary to increased insulin secretion |
| Meglitinide analogs | Repaglinide (Prandin®) Nateglinide (Starlix®) | • Lower risk of hypoglycemia than sulfonylureas.<br>• Meal based dosing may be beneficial for patients who vary the timing of their meals. Less hypoglycemia risk with meal delay. |
| Biguanides | Metformin (Glucophage®, Glucophage XR®) | • Not associated with hypoglycemia when used as monotherapy.<br>• Weight loss of 2 – 5 kg frequently seen, but actual cause of weight loss unknown.<br>• Take with meals and increase gradually to reduce GI side effects |
| Alpha-glucosidase inhibitors | Acarbose (Precose®) Miglitol (Glyset®) | • Not associated with hypoglycemia when used as monotherapy; but if used in combination, a low blood glucose must be treated with a form of glucose (glucose tablets) and not sucrose or starch since these medications inhibit carbohydrate absorption<br>• Most effective for postprandial hypoglycemia<br>• Gastrointestinal side effects (diarrhea, abdominal pain, flatulence) may be minimized by initiating at lowest dose and gradually increasing<br>• Take with first bite of meal (skip dose if skipping meal) |

*(Continued)*

Table 9
*(Continued)*

| *Diabetes Treatment* | *Medication* | *Nutrition and Weight Management Considerations* |
|---|---|---|
| Thiaolidinediones (TZDs) | Rosiglitazeone (Avandia®)<br>Piogliatzone (Actos®) | • Not associated with hypoglycemia when used as monotherapy<br>• Weight gain<br>• Mild to moderate edema |
| Insulin | | • As an anabolic hormone, insulin enhances fat storage and is often associated with weight gain as glycemic control improves<br>• Increased risk for hypoglycemia; could potentially increase eating for hypoglycemia prevention or treatment<br>Encourage pt to carry appropriate carbohydrate sources to treat hypoglycemia |
| Incretin mimetics | Exenatide (Byetta®) | • Administered by SQ injection within 60 minutes before a meal.<br>• Often results in decreased appetite, food intake and weight.<br>• Nausea is most common side effect.<br>• Hypoglycemia only if taken in combination with sulfonylurea or other diabetes agent causing hypoglycemia |
| *Obesity Treatment* | *Medication* | *Weight Management Consideration* |
| Sympathomimetic | Sibutramine (Meridia®) | • Used as an adjunctive therapy in pts with BMI $\geq$30 or $\geq$27 with other risk factors<br>• Appetite suppressant<br>• Adverse effects include increase in heart rate and blood pressure and thus should be monitored |
| Panreatic lipase inhibitor | Orlistat (Xenical®) | • Blocks 1/3 fat absorption<br>• Decrease in absorption of fat soluble vitamins; recommended to take daily multi vitamin supplement<br>• Side effects may occur with intake of >30% of calories from dietary fat, i.e., oily or loose stools, flatulence, fecal urgency |

*awaiting FDA approval
Adapted from Kulkarni, K. Diabetes Medications and Weight Management. On The Cutting Edge. 2003; 24(6):13–17 *(46)*.

As discussed in section 1, patients can be very influenced and confused by comments in the popular press regarding diets. Based on data from the National Weight Control Registry *(17)* and other research, the following general recommendations can be made for guiding patients who ask about weight loss programs:

- There is no one weight loss regimen that has been demonstrated to be most effective.
- Patients who are successful have reported the following common strategies: limiting a certain food (86%), limiting quantities (44%), eating breakfast daily (78%), and eating a diet containing only about 25% calories from fat.
- The use of a meal replacement supplement (such as a liquid formula) for one to two meals has been found helpful and acceptable by some patients *(48)*
- Successful losers are very physically active, reporting on average one hour per day of moderate intensity activity, such as brisk walking.
- Frequent monitoring appears to be linked with success: 44% of those in the NWCR weighed themselves at least once per day and 31% at least once per week.

For prediabetes and diabetes prevention, it is important to assess an individual's waist circumference as a measure of central obesity, which is more associated with metabolic risk. This is true even if BMI falls within the normal range. Women with a waist measurement of more than 35 inches or men with a waist measurement of more than 40 inches may have a higher disease risk than people with smaller waist measurements. To measure a waist circumference, place a tape measure around the bare abdomen just above the hip bone. The tape should be snug, but not compress the skin, and parallel to the floor. The patient should relax and exhale prior to measurement. When assessing either BMI or waist circumference measurements, some groups, such as Asians, should be evaluated using appropriate population standards.

Finally, to assist busy healthcare practitioners in treating overweight and obese patients, the NIH has prepared a useful Practical Guide as a resource *(47)*. It includes treatment algorithms, worksheets to use in patient counseling, such as weekly food and activity diary templates, and other useful tools.

## CONCLUSION

Medical Nutrition Therapy is a cornerstone of diabetes management. While its effectiveness to reduce A1C by 1-2% has been demonstrated when delivered by registered dietitians, all members of the medical care team need to understand the basic elements of MNT to reinforce the care plan. Patients with type 2 diabetes are particularly challenged by weight loss. However, there are other strategies besides a calorie-restricted diet that will improve metabolic measures. An understanding of the evidence based guidelines *(49)* will aid in the selection of realistic strategies for implementation (Table 10).

*It is easier to change a man's religion than to change his diet*. Margaret Mead

*It is better to talk about how far one has walked than how little one has eaten*. Elliott P. Joslin

**Table 10**
**Diabetes Nutrition Recommendations and Evidence Grading**

| | |
|---|---|
| Calories | • In overweight and obese individuals, modest weight loss (5–10%) improves insulin resistance. (1A)<br>• Weight loss diets should supply at least 1,000–1,200 kcal/d for women and 1,200–1,600 kcal/day for men(1A) |
| Protein | • In individuals with type 2 diabetes, ingested protein does not increase plasma glucose concentration but does increase serum insulin response. (1A)<br>• Reduction of protein intake to 0.8–1.0 g/kg body weight per day in individuals with diabetes and the earlier stages of chronic kidney disease (CKD) and to 0.8 g/kg body weight per day in later stages of CKD may improve measures of renal function such as urine albumin excretion rate and glomerular filtration rate. (1B) |
| Fat and Cholesterol | • Saturated fat <7% (1A)<br>• Two or more servings of fish per week (with the exception of commercially fried fish filets) provide recommended sources of omega-3 fatty acids (2B) |
| Carbohydrate | • Determining the percentages of carbohydrate, protein and fat will depend on treatment goals and individual circumstances. (2A)<br>• For weight loss, either low-carbohydrate or low-fat calorie restricted diets may be effective in the short term (upto 1 year) (1A) |
| Sweeteners | • Nonnutrititive sweeteners and sugar alcohols are safe when consumed within Acceptable Daily Intake levels established by FDA; (1A) |
| Fiber | • Evidence is lacking to recommend a higher fiber intake for people with diabetes than for the population as a whole. All adults are encouraged to achieve the USDA recommended levels of 14 g fiber per 1,000 kcals. (2A) |
| Glycemic Index | • The use of glycemic index and load may provide a modest additional benefit over that observed when total carbohydrate is considered alone. (1B) |

*(Continued)*

Table 10
*(Continued)*

| | |
|---|---|
| Sodium | • For patients with diabetes and symptomatic heart failure, dietary sodium intake of <2,000 mg/day may reduce symptoms (2A)<br>• In normotensive patients and hypertensive persons, a reduced sodium intake3 (e.g., 2,300 mg/day) with a diet high in fruit, vegetables and low-fat diary products lowers blood pressure. (1A) |
| Vitamins and Minerals | • There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes who do not have underlying deficiencies. Exceptions include folate for prevention of birth defects. (1A).<br>• Routine supplementation with antioxidants, such as vitamins E and C and carotene is not advised because of lack of evidence of efficacy and concern related to long term safety. (1A) |

Adapted from the American Diabetes Association 2006 Nutrition Recommendations *(49)*.

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# 9 Exercise as an Effective Treatment for Type 2 Diabetes

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***CONTENTS***



**Summary**

With the increasing incidence of type 2 diabetes and the associated comorbidity of obesity, there has been increased demand to develop effective treatment programs. Exercise has been traditionally associated with a number of health benefits, including increased insulin sensitivity, but remains an underused modality. Although certain contraindications exist for those individuals with health complications, exercise can be a safe and effective treatment for most people with type 2 diabetes. To date, the majority of research has focused on aerobic exercise, and suggests that low to moderate exercise intensity improves insulin sensitivity and glycemic control in patients with type 2 diabetes, especially those who are treated early in the disease. Some recent research has also supported the use of resistance exercise in type 2 diabetes. As with aerobic exercise, improvements in insulin sensitivity and glycemic control have been reported with moderate intensity resistance exercise. Both aerobic and resistance exercise should be incorporated into a weekly exercise program to take advantage of the exercise-specific adaptations that improve overall glucose disposal. Regardless of the type of exercise, both the American Diabetic Association and the American College of Sports Medicine agree that exercise should be taken at least 3 times per week, on nonconsecutive days. Based on the available research, regular exercise can play an integral role in the treatment of type 2 diabetes and can be prescribed to the majority of patients.

**Key Words:** Type 2 diabetes; aerobic exercise; resistance exercise; insulin sensitivity; glut 4.

## INTRODUCTION

The development of type 2 diabetes is multi-factorial, involving environmental as well as genetic components. Although altering some risk factors (i.e., age, genetics) is difficult, if not impossible, a large body of data indicates that a physically active lifestyle is a relatively effective intervention for treating the insulin resistance occurring with type 2 diabetes. In addition, exercise training also provides a means for increasing energy expenditure, which, when coupled with effective dietary practices, can produce desirable weight loss.

Although the health benefits of incorporating physical activity into one's daily regimen are apparent, the more subtle aspects of the actual exercise prescription to be used are not. Unfortunately, only one third of all patients with type 2 diabetes comply with the national physical activity goals set forth by the Center for Disease Control *(1)*. Recommendations from public health entities encompass a relatively wide range of exercise modes (i.e., walking, running, and resistance training), durations, frequencies (most days of the week versus every day versus

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3–4 d per week), and intensities (anywhere from walking to more intense jogging/running). These guidelines become even more complex for the person with type 2 diabetes, for whom certain types of exercise may be contraindicated owing to hypertension, heart disease, obesity, blood glucose control, medications, retinopathy, or peripheral neuropathy.

This chapter summarizes research describing the effect of either aerobic- (i.e., endurance) or resistance- (i.e., weight lifting) oriented exercise training on insulin action, leading to enhanced metabolic control, in patients with type 2 diabetes. This information will provide a foundation for the development of safe and effective exercise prescriptions. Although general contraindications for exercise will be discussed, a major assumption inherent in this chapter is that the diabetic subjects performing exercise were properly cleared by a physician for initiating physical activity.

## AEROBIC EXERCISE

Because type 2 diabetes is associated with hyperglycemia and insulin resistance, and skeletal muscle is a main source of glucose uptake *(2)*, clinical exercise research has focused on therapeutic methods of reducing elevated glucose levels and improving insulin action. The measured improvements in insulin action may be owing to either the chronic effects of training, or simply the residual effect of the last bout of exercise. Studies of healthy endurance trained males, as well as individuals with type 2 diabetes, have shown that improved insulin sensitivity is maintained up to 16 h after a single bout of exercise *(3,4)*, but may be diminished 60 h after the final exercise session during repeated days of exercise training *(5)*. In spite of this finding, glucose uptake is greater in aerobically trained skeletal muscle than in untrained muscle *(6)*. Therefore, to obtain optimal results, patients with type 2 diabetes should exercise multiple days per week, and thus obtain both the acute and chronic benefits of exercise.

Several definitions are important for the implementation of an aerobic-based exercise prescription. Exercise intensity is commonly reported as a percentage of an individual's maximal oxygen consumption ($VO_2$max). This is considered the most recognized measure of an individual's aerobic capacity, and is a strong indication of an individual's cardiopulmonary fitness level. Because the majority of exercise sessions in a clinical setting use heart rate to gauge exercise intensity, a general point of reference is that a moderate exercise intensity of 60% $VO_2$max generally equates to 70% of an individual's maximal heart rate *(7)*. If possible, maximal heart rate should be directly determined during a maximal exercise stress test. This test uses an incremental workload, and is commonly performed on a treadmill or stationary bicycle. For safety purposes, this assessment is performed under the supervision of a physician and a 12-lead EKG is monitored throughout. A direct measurement of maximal heart rate is considered more accurate than the value obtained using the age-adjusted maximal heart rate equation (220 -age).

### *Effects of Aerobic Exercise on Blood Glucose Concentration*

The most pronounced finding during and immediately after aerobic exercise in many type 2 diabetic patients is a decrease in blood glucose levels *(4,8,9)*. Unlike individuals with normal glucose metabolism, people with type 2 diabetes may experience an immediate decline in blood glucose levels with low to moderate exercise intensity of approx 40 min duration *(8,9)*. The cause of this phenomenon, which appears specific to this population, has been debated. Early speculation suggested that the decline in glucose was caused by the decreased hepatic production during exercise *(10)*. However, more recent research indicates that type 2 diabetic patients are capable of matching, if not exceeding, the glucose production of their healthy and obese counterparts during exercise *(11)*. Martin et al *(9)* reported that, after 40 min of cycling at 60% $VO_2$max, glucose uptake in the leg of patients with type 2 diabetes was twice that of nondiabetic controls, despite similar increases in splanchnic glucose output. The finding of greater glucose uptake in such patients has been reported by others *(8,11)* and likely contributes to the immediate decline in blood glucose levels exhibited in these individuals in response to aerobic exercise. It is important to note that, despite decrements in blood glucose levels in type 2 diabetic patients, blood levels still generally exceed those of healthy controls; therefore, exercise-induced hypoglycemia is not a common concern among these patients and physicians in most instances can safely recommended exercise as part of their therapeutic treatment of type 2 diabetes. Nonetheless, baseline glucose measurements should always be made before exercise,

and additional precaution is needed for those taking medication such as insulin and sulfonylureas, which could act synergistically with exercise to produce hypoglycemic conditions. Therefore, patients should be aware of baseline, exercise and recovery glucose levels, especially when commencing an exercise program.

Blood glucose levels return to baseline within hours of exercise cessation. The health benefits of these acute reductions in blood glucose remain unknown. It is possible that repeated transient reductions trigger a more permanent decline in resting blood glucose levels. However, inconsistencies have been reported with respect to the effect of aerobic training on preexercise hyperglycemic blood levels. Researchers have reported either decreases *(12,13)* or no change *(14–17)* in fasting blood glucose levels in response to aerobic training. Examination of this research indicates that frequency of exercise *(12,13)*, as well as early diagnosis of type 2 diabetes *(18)* may influence the ability of exercise training to decrease basal blood glucose levels. It appears that improvements in blood glucose levels can be achieved with low intensity exercise, as long as the frequency of exercise is high. Barnard et al *(12)* and Yamanouchi et al *(13)* reported that daily walking was a sufficient stimulus to decrease fasting blood glucose levels.

The effect of aerobic training on long-term glycemic control, as assessed by HbA1c measurement, has been evaluated, with inconsistent results. Some aerobic training studies have reported statistical improvements, with decreases in HbA1c typically in the 1–2% range *(19–22)*, although others have reported no change *(16,23,24)*. Part of the discrepancy in the findings is likely attributed to differences in exercise protocols, including differences in exercise intensity, duration and frequency. In addition, many of these studies used subjects on different antidiabetic medications, and some studies also included diet modifications. These are all factors that may have contributed to the variability in the results.

Although the prior discussion focused on the blood glucose response for low to moderate exercise intensity, it should also be mentioned that exercise at higher intensities can bring additional concerns. For the type 2 diabetic, exercise at high intensity (i.e., >80% $VO_2$max) can cause a hyperglycemic response during exercise and recovery owing to the exaggerated counter regulatory hormonal response of epinephrine and glucagon *(25)*. Exercise-induced hyperglycemia is of particular concern for those individuals with long-standing type 2 diabetes, where insulin production has been diminished.

### *Effects of Aerobic Exercise on Insulin Action*

The reported increase in insulin-mediated glucose uptake that occurs during and immediately after exercise has been well documented *(4,9)*. However, it has been more difficult to outline the effects of an endurance-oriented exercise training program on glucose dynamics through glucose tolerance tests. Some studies have suggested that as little as 7 d of aerobic training is sufficient to improve glucose tolerance *(22,26,27)*, although others have reported no training effect on this glycemic variable *(14,17)*. Based on these inconsistent findings, it is possible that the frequency of the training sessions, as well as the initial metabolic status of the individual may play a role. Studies that have demonstrated improvements in glucose tolerance typically use daily exercise at a moderate to high intensity in lean or newly diagnosed type 2 diabetic individuals *(22,27)*. In contrast, studies reporting no effect on glucose tolerance have typically used less frequent training in older, obese individuals with type 2 diabetes *(14,17)*. Despite variable results using both oral glucose tolerance tests (OGTTs) and intravenous glucose tolerance tests (IVGTTs) *(19,22,26)*, exercise training studies applying the gold standard measurement of insulin sensitivity, the hyperinsulinemic euglycemic clamp, have reported dramatic increases in whole body glucose uptake over a wide range of plasma insulin concentrations *(13,15,22,26)*.

Improved insulin action has been reported immediately after low *(28)* and high intensity *(25)* aerobic exercise. Bruce et al *(29)* compared exercise-induced improvements in insulin sensitivity in type 2 diabetic patients with healthy controls. Exercise training consisted of 8 wk of cycling at 70% $VO_2$max for 60 min, 3 times per week. Insulin sensitivity was measured at least 36 h after the last bout of exercise. These results may be a more accurate indicator of the effects of chronic exercise training, rather than showing residual effects from the last exercise bout. Type 2 diabetic patients were equally responsive to aerobic training, with similar relative increases in insulin sensitivity (~30%) when matched for age, body composition, and fitness levels. However, as with acute exercise *(4)*, chronic aerobic exercise does not appear to completely reverse the effects of diabetes because exercising type 2 diabetic subjects still had lower absolute insulin sensitivity (~60%) and glucose MCR then their healthy, exercising counterparts *(29)*.

Despite using a similar training protocol to Bruce et al *(29)*, Poirer et al *(23)* reported no improvements in insulin sensitivity in type 2 diabetic patients during 12 wk of training. However, when subjects were divided into 2 groups based on percent body fat, improvements in insulin sensitivity occurred in the nonobese type 2 diabetic subgroup. These findings support an earlier report by Ronnemaa et al *(18)* that only a certain subgroup of type 2 diabetics may achieve significant improvements in insulin sensitivity in response to exercise training. Based on this research, it appears that obesity and poor metabolic control (i.e., fasting plasma glucose >195 mg/dL) are barriers to improvements in insulin sensitivity in type 2 diabetic patients.

## Factors Influencing the Effects of Exercise on Insulin Sensitivity

The results of exercise studies in patients with type 2 diabetes demonstrate considerable variability. Exercise-induced insulin sensitivity is likely regulated by a number of factors, including the characteristics of the patient (i.e., age, health, and current treatment methods) and the type of exercise used. The following section discusses how some of these variables may impact attempts to improve insulin sensitivity in the type 2 diabetic.

**Exercise Intensity and Duration.** Obesity and lack of physical fitness in the diabetic patient may make low intensity exercise a more practical and attractive option, compared to higher intensity work. In fact, moderate intensity exercise may be just as beneficial for improving insulin sensitivity as higher intensity exercise, even in young individuals *(30–32)*. O'Donovan et al *(32)* reported that, in a sedentary population, 24 wk of aerobic training at 60% $VO_2$max produced similar improvements in insulin sensitivity to training at a higher intensity (80% $VO_2$max), when controlling for energy expenditure. Based on these findings, the authors concluded that exercise involving an expenditure of 400 kcal per session, 3 times per week, was sufficient to increase insulin sensitivity, regardless of whether the exercise intensity was moderate or high.

Burnstein et al *(28)* reported increased insulin sensitivity 1 h after a 60 min walk in obese type 2 diabetic subjects. In addition, other studies using patients with type 2 diabetes have demonstrated increased glucose clearance with daily walking *(13)* and improved insulin sensitivity when low intensity training was added to sulfonylurea therapy *(33)*. These findings support the concept that metabolic benefits can be achieved with relatively low intensity aerobic exercise.

Thus, low intensity exercise, such as walking, may provide adequate metabolic improvements and be a safe, practical option for individuals with type 2 diabetes. This finding is encouraging, especially for individuals who may not tolerate higher intensity exercise. However, it is likely that diabetic patients with more severe insulin resistance or older individuals, as discussed subsequently, may need to perform exercise sessions of 1 h in duration using moderate intensity exercise to obtain benefits.

There are few studies that examine the effects of exercise duration on insulin sensitivity in type 2 diabetic patients. However, research conducted by Houmard et al *(30)* with sedentary, obese individuals indicates that an exercise duration of 170 min/wk was more effective improving insulin sensitivity than 115 min/wk, regardless of exercise intensity and volume. Future research is needed to determine if this relationship also exists in patients with type 2 diabetes.

**Age.** Insulin sensitivity has been reported to decrease with age, with an average reduction of 8% per decade after age 20 in both men and women *(34)*. It has been suggested that increased physical activity may attenuate this trend toward insulin resistance. Unfortunately, few studies have investigated the effects of aerobic exercise on insulin sensitivity or glycemic control in the older (i.e., >60 yr) type 2 diabetic population. Those studies that have been conducted have reported no change in glucose tolerance *(14,35)* or insulin sensitivity *(35)*. It is unclear if the lack of improvement is specifically related to age or to more advanced, and irreversible, metabolic dysregulation as a consequence of longstanding diabetes. In addition, it should be noted that lack of randomization, use of nonsupervised exercise sessions, and low adherence rates may have biased these results. Therefore, recent studies in older, healthy subjects are summarized below to illustrate the effect of age per se on insulin action.

DiPietro et al *(36)* recently reported that improvements in insulin sensitivity were observed with high intensity training (80% $VO_2$max), but not with moderate (65% $VO_2$max) or low intensity (50% $VO_2$max) training in healthy, nonobese, older (73 ± 10 yr) women. Similarly, Short et al *(34)* reported that middle aged and older

healthy individuals did not demonstrate improvements in insulin sensitivity in response to aerobic exercise at a moderate intensity (70–80% max heart rate), despite improvement in GLUT 4 content and mitochondrial enzyme activity.

It is possible that, in addition to the effects of exercise intensity, energy expenditure and exercise duration may play a role in the insulin responsiveness of older type 2 diabetic patients. Although the exercise program described by Short et al *(34)* only included exercise sessions of 20–40 minute duration, Evans et al *(37)* reported that exercise of 1 h duration at a slightly higher exercise intensity (83% max heart rate) was sufficient to increase insulin action (29% increase in glucose disposal rate relative to insulin concentration during the hyperglycemic clamp), in individuals 77–87 yr old. The improved insulin sensitivity was based on an average increase in total energy expenditure of 400 kcal/d. In comparison, DiPietro et al *(36)* reported increases in total energy expenditure of 41 and 102 kcal/d during the low and moderate intensity programs, respectively. Therefore, it is possible that older individuals can increase insulin sensitivity, but moderate aerobic intensity, with sufficient exercise duration, may be needed to increase energy expenditure significantly. No data are yet available to determine if such exercise recommendations are applicable specifically to older, type 2 diabetic patients.

**Fitness Level and Weight Loss.** In addition to the increased insulin sensitivity observed with aerobic training, improvements in aerobic capacity and body composition are also noted. These findings have prompted the speculation that enhancement of either of these variables may predict improvement in the metabolic control of type 2 diabetes. In general, studies observing improved insulin sensitivity have reported increases in $VO_2$ max of 15% *(15,22)*. However, it is apparent that improved $VO_2$ max does not guarantee enhanced insulin sensitivity, as other studies showing similar relative improvements in $VO_2$max have demonstrated no statistical improvement in insulin action *(38,39)*. In addition, improved insulin sensitivity has been demonstrated despite the absence of changes in aerobic capacity *(27)*. Therefore, it is likely that the adaptations responsible for improvements in aerobic capacity are not the sole cause of enhanced insulin sensitivity. Similarly, weight loss is not required for improvements in either glycemic control or insulin sensitivity *(20,23,29)*. A study using multiple regression analysis demonstrated that walking, without weight loss, had a positive effect on insulin sensitivity *(13)*. Changes in body composition resulting in decreased adipose tissue, rather than overall weight loss, may have a greater influence on insulin action. Mourier et al *(20)* reported that improvements in insulin sensitivity were correlated with the loss of visceral adipose tissue in patients with type 2 diabetes whose weight was not altered with 8 wk of aerobic training.

**Diet and Medication.** Two other factors that likely contribute to the observed variability in responses to exercise training are dietary modification and the use of antidiabetic drugs. In many instances, diet recommendations are made in addition to exercise as part of an overall lifestyle modification. The addition of regular exercise to dietary therapy improves glycemic control and insulin sensitivity compared to diet alone *(13,15)*. In addition, it has been suggested that exercise, apart from negative energy balance, is effective in improving insulin sensitivity *(40)*. Trovati et al *(22)* reported that daily walking improved insulin sensitivity in nonobese type 2 diabetic patients, despite the addition of 400 kcal per day to their diet to compensate for calories burned during the daily exercise regimen.

Unfortunately, no known studies have directly compared the effectiveness of antidiabetic medication versus regular exercise in type 2 diabetic patients. Many studies have not been able to control for medication use or dietary intake when examining the value of regular exercise, which has likely contributed to the confusion over the effectiveness of exercise alone as a therapeutic model for type 2 diabetic patients. However, comparing the results from separate studies has highlighted the usefulness of regular exercise. Individuals following a regular exercise program can have similar improvements in insulin sensitivity and glycemic control to those produced by the use of some oral antidiabetic medications. For example, Bailey et al *(41)* reported that in type 2 diabetic patients, 24 wk of high dose (3 g/d) Metformin (MET) or a combination treatment of Rosiglitizone (RSG) and MET improved insulin sensitivity by 7% and 34%, respectively. In comparison, regular exercise has been reported to increase insulin sensitivity by approx 30% in patients with type 2 diabetes. Furthermore, the Diabetes Prevention Program Research Group *(42)* reported that a lifestyle intervention program including diet and exercise was more effective than metformin in preventing type 2 diabetes in individuals considered at risk. Results from this randomized,

multi-center clinical trial demonstrated a risk reduction of 58% and 31% in the lifestyle intervention group and metformin group, respectively, in comparison with the placebo group.

Thus, based on the improvements in insulin sensitivity, glycemic control, and the many other health benefits associated with exercise, regular exercise may be effective in the prevention and early treatment of diabetes. In addition, regular exercise may serve as a useful adjunctive therapy in combination with medication for those with advanced diabetes.

## *Mechanisms of Improved Insulin Action with Aerobic Exercise*

Glucose uptake occurs through insulin-dependent and insulin-independent mechanisms *(2)*. A number of possible explanations have been suggested to account for the immediate increase in glucose uptake during exercise, including exercise-induced increases in blood flow and capillary surface area *(43)*. In addition, significant hyperglycemia itself may promote uptake through a mass action effect *(8,11)*.

The effect of exercise to increase glucose uptake during and immediately after exercise appears to be mediated via changes in the main glucose transporter in skeletal muscle, GLUT4. When skeletal muscle is in an unstimulated state, the majority of GLUT4 protein resides in storage sites within the muscle fiber. It has been suggested that at least 2 separate intracellular "pools" of GLUT4 exist within the muscle fiber, one stimulated by insulin and one by muscle contraction *(44)*. Although people with type 2 diabetes have lower absolute levels of GLUT4 protein compared to their healthy counterparts, they appear to have a similar capacity to translocate GLUT4 to the plasma membrane in response to acute aerobic exercise *(45)*. Therefore, it appears that the capacity for acute exercise-induced recruitment of GLUT4 from intracellular compartments remains intact in the type 2 diabetic patient.

Although acute mechanisms such as increased blood flow and translocation of GLUT4 could be involved in the immediate increase in glucose uptake in the type 2 diabetic patient, the explanation of the long term improvement in insulin-mediated glucose uptake post exercise is less clear. Sustained increases in GLUT4 protein content occur after repeated bouts of exercise, and therefore this training effect could account for the improved glucose clearance in trained versus untrained muscle *(46)*. In addition, individuals with type 2 diabetes often have depressed insulin receptor tyrosine kinase and phosphoinositide kinase-3 (PI3K) activity *(47)*. Houmard et al *(48)* reported that as little as 7 d of aerobic training elicited increased insulin sensitivity associated with increased insulin stimulated PI3K activity in healthy men. However, preliminary studies suggest that the effect of exercise on the insulin signaling pathway may be impeded in insulin resistant patients with type 2 diabetes *(49,50)*. Therefore, it is possible that other intracellular pathways are activated in type 2 diabetes, resulting in exercise-induced improvement in glucose uptake *(51)*.

## *Risks and Complications Associated with Aerobic Exercise*

Before initiating an exercise program, patients with type 2 diabetes should undergo a thorough medical evaluation. This evaluation should include an assessment of glucose control, questioning for any history of recurrent hypoglycemia or hypoglycemia unawareness, review of prescribed medications, and an examination for the presence of possible complications (i.e., cardiovascular disease, peripheral neuropathy, retinopathy, and/or nephropathy). In addition, based on the age of the individual and the duration of diabetes, an exercise stress test is advised. The American College of Sports Medicine (ACSM) and the American Diabetes Association (ADA) recommends that all type 2 diabetic patients over the age of 35 have a stress test performed before participating in an exercise program *(52,53)*. The following possible areas of concern should be considered when prescribing exercise for patients with type 2 diabetes.

### Exercise-Induced Hyperglycemia

The potential for exercise-induced hyperglycemia is a concern for type 2 diabetic patients, especially those with long-standing diabetes or those participating in high intensity exercise (>80% $VO_2$max). Moderate to high intensity exercise requires increased glucose use to meet energy demands. As a result, counteregulatory hormones such as epinephrine and glucagon are released and increase the production and availability of glucose. In the healthy individual, there is typically a small hyperglycemic response that occurs during exercise and recovery, which results in a hyperinsulinemia to allow glucose concentrations to return to basal levels. However, in type 2 diabetes there is often an exaggerated response by epinephrine and glucagon during high intensity exercise, which

can produce hyperglycemia *(25)*. In addition, patients with long-standing type 2 diabetes often lack the ability to release insulin to offset the exercise-induced hyperglycemia, which may result in dangerously high blood glucose levels. Therefore, blood glucose should be measured at baseline, during exercise, and throughout 1 h of recovery in the type 2 diabetic patient, especially when initiating an exercise program.

### Cardiovascular Disease

Patients with diabetes are at increased risk of myocardial infarction. Therefore, an exercise prescription should be under physician supervision if abnormalities are observed during the initial exercise stress test. Diabetic patients with known coronary artery disease, but without cardiac ischemia or signs of heart arrhythmias, may participate in supervised, approved exercise.*(54,55)*.

### Autonomic Neuropathy

Autonomic neuropathy can decrease maximal heart rate and blood pressure, as well as elevate resting heart rate. A physician should evaluate all patients with this complication before an exercise program is started owing to increased risk of postural hypotension and the potential to miss early warning signs of ischemia *(55)*. Owing to the lower fitness level of individuals with autonomic neuropathy *(56)*, the exercise prescription should generally include low-intensity daily activities *(55)*. In addition, owing to the effects of autonomic neuropathy on heart rate and blood pressure, it is advised that a rating of perceived exertion (RPE) be used to monitor exercise intensity. The Borg RPE scale is the most frequently used method of determining exercise intensity *(57)*. With its use, the exerciser is told to subjectively rate his or her perceived exertion on a scale that ranges between 6 (no exertion) and 20 (maximal exertion). Typically, moderate intensity exercise elicits ratings between 12 and 14. It is also suggested that exercise sessions avoid hot or cold environments because individuals with autonomic neuropathy tend to have impaired thermoregulation *(58)*.

### Peripheral Neuropathy

Peripheral neuropathy is of concern to the exercising type 2 diabetic patient because the loss of distal sensation to the lower legs and feet can lead to musculoskeletal injury, or cutaneous injury or infection. Individuals with peripheral neuropathy should participate in nonweight- bearing activities such as cycling or swimming *(55)*. Proper footwear (i.e., gel or air running shoes) and daily examination of the feet is necessary when weight-bearing activities are included, to detect any foot lesions that could lead to serious infection.

### Nephropathy

It is unclear how the acute exercise-induced increase in blood pressure might affect nephropathy, but it is suggested that exercise training may control factors (i.e., blood pressure and blood glucose) thought to contribute to the progression of this problem. Individuals with diagnosed nephropathy should avoid exercise causing systolic blood pressure to rise to values above 180 mmHg *(55)*. Therefore, high intensity aerobic and resistance exercise should be avoided. Maintenance of proper hydration levels is imperative in individuals with nephropathy.

### Retinopathy

Because increasing blood pressure in the exercising diabetic patient is a concern, and might adversely affect retinopathy, all type 2 diabetic patients with retinopathy should be evaluated by an opthalmologist before starting an exercise program. If proliferative or severe retinopathy is present, the individual is generally instructed to avoid high intensity exercise or exercise involving jarring movement, such as high-impact aerobics or activities that involve lowering the head such as yoga or gymnastics *(53)*. Instead, low intensity exercise, such as walking or stationary cycling, is recommended.

## RESISTANCE EXERCISE

Resistance-oriented exercise training can have positive effects on glucose disposal, insulin action, and lipid metabolism. Improvements in insulin sensitivity and glucose disposal in normal *(59)*, insulin resistant *(60)*, and type 2 diabetic populations *(61,62)* have been shown following resistance training programs. As little as one

resistance exercise session may improve insulin action, as evidenced by a decreased insulin response during an oral glucose tolerance test with no change in glucose response *(63)*, although greater benefits appear to accompany exercise training *(64,65)*. Most studies of resistance exercise in type 2 diabetic patients utilize a progressive intensity program, increasing load as muscular strength increases, to maintain exercise intensity. Several groups have begun to examine the additional benefits of high intensity resistance training, particularly in elderly type 2 diabetic patients *(61,66,67)*. At present, it is difficult to determine an ideal training intensity owing to the lack of continuity among study assessments. Nevertheless, no adverse effects have been reported in the general diabetic population who reach training intensities of 80–85% of the maximum amount of weight an individual can lift at one time (generally referred to as the 1 repetition maximum or 1 RM), even among the elderly *(67)*. With a 90–100% compliance rate reported *(61,67,68)*, resistance exercise represents an often underused preventative and treatment modality for type 2 diabetes.

### *Effects of Resistance Exercise on Blood Glucose Concentration*

It is well accepted that resistance exercise improves glycemic control *(69)*. Type 2 diabetic patients show improvements in fasting blood glucose concentrations after as little as 10 wk of moderate to high intensity resistance exercise (50–85% of 1RM), performed 3 d/wk *(16,61,67,68)*. Some report improvements in HbA1c concentrations after 10 wk of a similar intervention, although most observe significant improvements following a protocol of longer duration *(16,66–68)*. In these studies, patients with type 2 diabetes performed progressive resistance training at a moderate to high intensity 3 d/wk for 4–6 mo. On each day of exercise, patients performed 1–2 sets of 10–15 repetitions to fatigue. A similar protocol *(64)* used a continuous glucose monitoring system (CGMS) to examine changes in glucose regulation during a 48-h period, and noted a 16% improvement in mean blood glucose levels. Nevertheless, others have reported nonsignificant changes in fasting glucose *(70)* and HbA1c *(70,71)* despite similar subject populations and exercise protocols. The reason for this discrepancy remains unknown, although the large range in exercise intensity and/or differences in training duration used in these studies may have played a role.

Initial concern that high intensity resistance exercise could impair muscle mediated glucose uptake, as a result of acute muscle damage, has not been supported by research. Improved glycemic control (12–15%) during oral glucose tolerance tests within 24 h of the last exercise bout have been reported in type 2 diabetic patients as well as subjects with impaired glucose tolerance *(65,72)*. Results from an oral glucose tolerance test performed 18 h after exercise demonstrated that a single resistance exercise bout, consisting of 3 sets of 10 repetitions using 7 exercises, improved insulin profiles but did not affect glucose in either young healthy individuals or older patients with type 2 diabetes *(63)*, indicating an improvement in insulin action.

### *Effects of Resistance Exercise on Insulin Action*

Several reports have used the hyperinsulinemic-euglycemic clamp to determine insulin sensitivity in type 2 diabetic patients following resistance exercise training. Insulin sensitivity improved by 48% after only 4–6 wk of progressive resistance exercise (5 d/wk) in nonobese patients with type 2 diabetes (BMI = 22 kg/m$^2$), using 2 sets of 10 and 20 repetitions for upper and lower body exercises, respectively *(62)*. Similarly, 6 mo of resistance training in insulin resistant patients training 3 d/wk, using 1–3 sets of 8–15 repetitions, showed a 10% improvement in insulin sensitivity *(73)*.

## Factors Influencing Insulin Sensitivity with Resistance Exercise

**Exercise Intensity and Training Duration.** When prescribing the level of intensity for resistance exercise, a common method is to use a percentage of the 1 RM. As described earlier, 1 RM refers to the maximum amount of weight an individual can lift successfully one time. Owing to safety implications a "true" 1 RM is not usually performed, and instead can be estimated as described by Wathen *(74)*. Briefly, a light weight is initially used and the patient is instructed to perform as many repetitions as safely possible with it. Based on the number of completed repetitions, a predictive 1-RM table can calculate what the patient's estimated 1 RM load would be for that particular exercise. Once this is achieved, the appropriate load can be selected based on the exercise intensity required. As a general point of reference, resistance exercise of moderate intensity (50–70% 1 RM) usually equates to 8 to 12 repetitions.

Most studies examining resistance exercise training in type 2 diabetes employ a moderate exercise intensity (50–70% 1 RM) *(62,70–72)*, although it appears that high intensity resistance training (70–85%) is also well-tolerated *(61,66,67)*. Reductions in HbA1c were similar following 4–6 mo of high intensity resistance exercise (approx 9 upper and lower body exercises, 3 d/wk, of progressive resistance at 50–85% 1 RM, using approx 3 sets of 8–10 repetitions) *(66,67)*, and 4 mo of moderate intensity resistance exercise (10 upper and lower body exercises, 3 d/wk, 1–2 sets of 10–15 repetitions of progressive resistance to fatigue) *(64)*. For example, Dunstan et al *(67)* demonstrated reductions in HbA1c from 8.1% to 6.9%, whereas Cauza et al *(64)* reported mean reductions in HbA1c from 8.3% to 7.1% with a lower intensity program, although exercise intensity in this latter study was not explicit and may have bordered on high intensity during certain training sessions. The lack of specific criteria for classifying exercise intensity in these studies makes it difficult to ascertain potential differences in intensity-related outcomes. Additionally, no studies have directly compared the effects of different intensities of resistance training in patients with type 2 diabetes; therefore, there is no conclusive evidence that high intensity resistance training provides greater improvement in glucose control. Resistance exercise training has been shown to result in large improvements in insulin sensitivity within 4–6 wk *(62)*. In a controlled study of normal weight (mean BMI of 22 kg/m$^2$) type 2 diabetic patients, moderate intensity resistance exercise (approx 40–50% of 1RM, 5 d/wk) improved insulin sensitivity by 48% during a hyperinsulinemic-euglycemic clamp measurement performed 2 d after the last exercise bout *(62)*. Ibañez et al *(61)* observed similar improvements in insulin sensitivity (46%) in type 2 diabetic patients using a hyperinsulinemic-euglycemic clamp 24 h after completion of a 16 wk training session. In spite of the longer training session, the latter experiment only employed resistance exercise 2 d/wk, but involved a much higher intensity (70–80% 1RM). The similar outcome between these two studies is likely explained by similar improvements in muscular strength (approx 17%). These data indicate that exercise intensity and the duration of training may be variables affecting the extent of improved glycemic control, secondary to their effects on muscle strength and/or hypertrophy.

**Duration of Type 2 Diabetes.** At present, there are insufficient data to determine the benefits of beginning a resistance training program as early as possible after diagnosis of type 2 diabetes. Most reports of resistance training in type 2 diabetic patients include those who have been diagnosed for at least 3 yr (average of 8 yr) *(16,64,66–68,70,71)*. However, one study of overweight (BMI = 28.3 kg/m$^2$) elderly men (67 yr old) with newly diagnosed type 2 diabetes showed improvements in insulin sensitivity similar to those with a longer history of diabetes *(61)*. Ryan et al *(73)* have reported that older individuals with more pronounced insulin resistance show greater improvements than those with less severe insulin resistance following resistance exercise training (3 d/wk for 6 mo, performing 1–3 sets of 8–15 repetitions on each day of exercise). This is different from aerobic-oriented exercise training, in which those patients with more severe insulin resistance show little improvement in insulin sensitivity compared with patients having less severe insulin resistance *(20)*. This implies that similar improvements in insulin sensitivity can be achieved in both newly diagnosed patients and those who have had diabetes for many years. This also implies that patients who have had type 2 diabetes for a longer duration may benefit from resistance training, whereas aerobic training has not been consistently successful in improving glycemic control in such patients. In addition, for patients in a prediabetic state (i.e. impaired glucose tolerance) data demonstrating a complete reversal of impaired glucose tolerance following 4 mo of either moderate resistance or aerobic training *(60)* should encourage practitioners to prescribe resistance and/or aerobic training as soon as diabetes diagnosis takes place, or if possible, when the individual is considered at risk for the development of type 2 diabetes (i.e., relatives of type 2 diabetics).

### *Additional Benefits of Resistance Exercise*

Benefits of moderate or high intensity resistance training in patients with type 2 diabetes include improved mobility as well as reduced adiposity *(75)*. Such improvements are generally observed in those who also experience increases in muscle strength and/or size, generally without a change in body weight *(61,62,66,71)*. This can be achieved at intensities of 60–100% of 1 RM *(75)*. Resistance exercise may also be tolerated by untrained or obese individuals who have difficulty performing aerobic exercise *(66,76)*. Several studies have examined the safety and efficacy of resistance training at higher exercise intensities (70–85% 1RM) in older individuals with type 2 diabetes (60–80 yr old). These supervised exercise programs have produced high rates of compliance

(88–99%), improvements in glycemic control (5–15%), and little to no adverse effects *(61,66,67)*. One report found, however, that compliance rates and recorded improvements in HbA1c concentrations may decline when exercise is performed at home or in an unsupervised environment, despite maintenance of muscular strength *(77)*. Overall, when performed on a regular basis, in a supervised environment, resistance exercise may prove at least as, if not more beneficial than other treatment methods (i.e., aerobic exercise, pharmaceutical treatment) for obese and older patients.

When accompanied by dietary restriction, resistance exercise training may also help to maintain or even improve muscle mass that is typically lost owing to energy deficit *(55)*. This is of potential benefit, not only by maintaining the mass of tissue available for glucose uptake, but also by maintaining mobility and strength, particularly in older individuals, who tend to lose muscle mass. Additionally, exercise training, when used in conjunction with dietary restriction, is more effective than diet alone for the reduction of fasting blood glucose levels *(67)*.

### *Mechanisms of Improved Insulin Action with Resistance Exercise*

The improvements of glycemic control following resistance training have often been attributed to the accompanying muscle hypertrophy, which effectively increases the tissue mass responsible for glucose uptake. Despite a high positive correlation between increases in lean body mass and insulin action, the magnitude of change is much greater for glucose disposal than body composition, indicating that a direct causal relationship does not exist *(69)*. Holten et al *(76)* have shown that 6 wk of 1-legged resistance training at 70–80% of 1RM in type 2 diabetic patients improved insulin action without a concomitant increase in muscle mass. Blood flow was increased in the trained leg versus the untrained leg, while the rate of glucose uptake remained unchanged. The authors concluded that cellular glucose extraction may have increased; otherwise greater blood flow would have resulted in decreased glucose uptake. Indeed, glycogen stores were elevated in the trained leg compared with the untrained leg. Muscle biopsy analysis revealed increased protein kinase B (PKB) levels in the trained leg, which is involved in glycogen synthase activity and possibly GLUT-4 translocation. Glycogen synthase and GLUT-4 protein contents were also increased with resistance training. Together, these data indicate that, as with aerobic training, there may be a direct effect of resistance training on insulin action at the level of the skeletal muscle cell, independent of changes in muscle mass. It is also important to note that these changes in PKB protein content were independent of changes in the oxidative capacity of the muscle *(76)*. It is thought that aerobic exercise-induced GLUT-4 translocation is mediated, in part, by AMPK and cytosolic calcium levels, which also stimulate muscle oxidative capacity *(69)*. The authors hypothesized that the cellular response that enhance insulin action in skeletal muscle following resistance exercise are distinct from those of aerobic exercise *(69)*. Further research is necessary to determine if this is so and whether the addition of resistance exercise to an aerobic exercise program would provide added improvements to insulin sensitivity via a separate cellular mechanism.

### *Risks and Complications Associated with Resistance Exercise*

Resistance exercise training introduces additional concerns, including the risk of cardiac ischemia and/or hypertension, but, when carefully supervised, this type of exercise can provide exceptional benefit with little to no adverse effect. Nevertheless, as with aerobic exercise, there are contraindications to resistance exercise for the type 2 diabetic patient.

One of the main concerns for diabetic patients is an elevation in blood pressure during or after a resistance training bout. However, although transient increases in blood pressure are often observed during a single repetition, particularly at higher intensities, blood pressure generally returns to baseline values or lower within 1–2 s after activity in healthy individuals *(78)*. In fact, a decrease of 5–15% in both systolic and diastolic blood pressures occurs following 4–6 mo of moderate and high intensity resistance training *(16)* even in older type 2 patients, averaging 67 yr old *(66,67)*. These decreases in resting and postexercise blood pressures are similar to those following 4 mo of aerobic training *(66)*.

For diabetic patients with other clinical manifestations of diabetes, such as cardiovascular disease or retinopathy, there are no consistent data regarding resistance exercise. A pretraining exercise stress test should be performed on those patients with risk factors for CAD to rule out ischemia, arrhythmias, or an exaggerated hypertensive response to exercise *(75)*. Load or weight bearing exercise is contraindicated for patients with peripheral vascular disease or peripheral neuropathy *(55)*. Resistance exercise may provide a beneficial exercise alternative. Patients

may perform many exercises in a seated position without putting additional pressure on the lower extremities. Nevertheless, it is still necessary to assure that proper footwear is used and that feet are periodically examined for sores and injuries *(55)*. There is no evidence to suggest that resistance exercise exacerbates the blood pressure-induced progression of nephropathy, although, as a precautionary measure, ACSM recommends that systolic blood pressures do not exceed 180–200 mm Hg during or after exercise, as is the case with aerobic exercise *(55)*. Resistance exercise in these patients may even improve muscle mass and nutritional status for those on a low protein diet *(75)*. For patients with cardiovascular disease, resistance exercise may be safer than aerobic exercise because of the lower heart rate and rate-pressure product (indicator of myocardial oxygen consumption: heart rate multiplied by systolic blood pressure) responses to resistance exercise *(79)*. For patients with less severe or moderate retinopathy, exercise intensities should be kept at a minimum *(55)*. Although there are no data proving that exercise of any type will worsen the condition, the ACSM recommends that low intensity aerobic exercise may be performed by some individuals with retinopathy, but for patients with more severe retinopathy, motions that cause large increases in blood pressure, such as putting the head down or the arms over the head, are not advised *(55)*. A general consensus of the resistance training literature is that low intensity resistance exercise may be tolerated by some patients with mild, nonproliferative retinopathy, although the effect of resistance exercise on intraocular pressure is not known *(75)*. All patients should avoid performing the valsalva maneuver or near maximal lifts.

## COMBINED AEROBIC AND RESISTANCE TRAINING

Recent recommendations by the ACSM and the ADA suggest that a combination of aerobic and resistance exercise be included in an exercise prescription *(53,55)*. These recommendations are based on the conclusion that improvements in insulin sensitivity can result from exercise-specific adaptations. Poehlman et al *(80)* have shown that the increase in lean body mass associated with resistance exercise contributes to increased glucose disposal. In contrast, improvements in glucose disposal observed with aerobic training are owing to improvements in the intrinsic capacity of the muscle because these improvements are independent of changes in lean body mass *(80)*. A combination of aerobic and resistance exercise training might therefore result in the physiological benefits of both types of exercise, and as a consequence the greatest degree of insulin-mediated glucose disposal.

There are few studies that have evaluated the benefits of combined exercise training in the diabetic population. Most studies examining the addition of resistance exercise to aerobic exercise programs have found beneficial results over aerobic exercise alone *(16,81)*. However, the majority of these have included greater overall exercise workloads during combined exercise, therefore potentially biasing the results.

One randomized 16-wk study controlled for energy expenditure between a combined aerobic and resistance training group and a group only participating in aerobic exercise *(24)*. Although there was no significant change in glycosylated hemoglobin, insulin action was significantly increased in type 2 diabetic subjects participating in combined aerobic and resistance training, but not aerobic training. Tokmakidis et al *(82)* also reported beneficial results; improvements in glucose tolerance, insulin sensitivity and glycemic control were found in postmenopausal women after only 4 wk of supervised aerobic and resistance exercise, with additional improvements at 16 wk.

Although both studies used postmenopausal females, only Tokmakidis et al *(82)* reported improvements in glycolated hemoglobin after 4 wk of combined training. It is possible that the design of the cross-training program needs to be considered. Subjects in the Cuff et al *(24)* study completed 3 d a week of circuit training where both aerobic and resistance exercises were completed on the same day. In contrast, subjects in the Tokmakidis et al *(82)* study completed 2 d of resistance exercise and 2 d of aerobic exercise on separate days. It may be too fatiguing for individuals with a low exercise tolerance to combine both types of exercise within one session, limiting the ability to maintain adequate exercise intensity and therefore minimizing the exercise benefits. In contrast, if individuals are capable of completing a fairly high exercise volume, circuit training has been reported to reduce fasting blood glucose levels as well as glycosylated hemoglobin levels within 8 wk *(83)*. Thus, depending on the specific prescription, improvements in diabetes control may result from a combination of aerobic and resistance exercise. This type of training may also be attractive to the diabetic patient looking for a program with a fair amount of flexibility and variety.

## EXERCISE RECOMMENDATIONS

All type 2 diabetic patients should undergo initial medical screening before the implementation of an exercise program. The following recommendations are directed towards those patients who are otherwise healthy or have minimal coexisting health complications, and have been medically cleared for exercise. A summary of these recommendations has been provided in Table 1. It is important to note that these recommendations are based on the notion that the type 2 diabetic patient has been previously screened by a health care professional for potential contraindications to exercise. These recommendations should be considered goals for the individual and it is assumed that the exercising person with type 2 diabetes will likely start at a lower exercise duration, frequency and potentially intensity to build an exercise tolerance before the exercise program reaches these goals. It is imperative that the individual is carefully monitored during the commencement of an exercise program including the monitoring of blood glucose at baseline, as well as, during and after exercise. The health care provider should then regularly monitor the patient as his or her program advances to assure that potential exercise and nonexercise related complications are diagnosed early, and appropriate modifications to the exercise program are implemented as required. As exercise tolerance increases, modifications in the exercise program should be made, initially focusing on increasing exercise duration and frequency *(52)*.

### *Aerobic Exercise Recommendations*

#### Aerobic Exercise Intensity

Currently, the ACSM recommends the use of low to moderate exercise intensity for the type 2 diabetic patient *(55,84)*. Low intensity aerobic exercise can be used by the majority of patients, including those with minor coexisting conditions, when supervised by a medical professional (Grade: 1B). For optimal benefits in glycemic control and insulin action, many recommend that aerobic exercise of moderate exercise intensity be prescribed for the many type 2 diabetic patients with no major health complications (Grade: 1B)

Low intensity aerobic exercise may not result in metabolic benefits in older individuals and patients who have longstanding diabetes. Therefore, when medically advisable, we recommend that these individuals start with a low intensity program and gradually increase to a moderate intensity program to obtain improvements in glycemic control and insulin sensitivity (Grade: 1C).

In addition, it is our recommendation that exercise intensity be monitored by heart rate, blood pressure and RPE. The use of an RPE scale is especially important when monitoring the exercise intensity of patients with autonomic neuropathy *(84)*.

#### Aerobic Exercise Frequency

The ACSM recommends that people with type 2 diabetes participate in at least 3 nonconsecutive exercise sessions per week *(55)*. Based on findings that exercise-induced improvements in glycemic control and insulin sensitivity may be lost within 72 h of the last exercise bout, it is also recommended that moderate-intensity

**Table 1**
**Summary table of exercise recommendations for the type 2 diabetic patient with no exercise contraindications**

| *Exercise modality* | *Exercise intensity* | *Exercise duration* | *Exercise frequency* | *Grade* |
|---|---|---|---|---|
| Aerobic exercise<br>-walking<br>- cycling<br>- swimming | Moderate Intensity (i.e., 70% of individual's maximal heart rate or 12–14 on the Borg RPE scale) | 30–60 min | 3 nonconsecutive d/wk | 1B |
| Resistance exercise | Moderate Intensity (50–70% 1 RM) | Eight exercises, 12–15 reps, 2–3 sets, 1–2 min rest between sets | 3 nonconsecutive d/wk | 1B |
| Cross-training | Similar to that described above | 60 min | 3 nonconsecutive d/wk | 2A |

RPE, rating of perceived exertion; 1 RM, 1 repetition maximum.

exercise be performed at least 3 times per week on nonconsecutive days (Grade: 1B). It is recommended that those individuals who are performing lower intensity aerobic exercise (e.g., walking) perform this exercise 5 d per wk, with the long-term goal of daily sessions (Grade: 1B). Daily physical activity is recommended for any type 2 diabetic patient who wants to obtain the largest improvement in glycemic control (Grade: 2A).

## *Resistance Exercise Recommendations*

### Resistance Exercise Intensity

ACSM recommendations for resistance exercise state that type 2 diabetic patients should complete approx. 8 exercises involving major muscle groups, and that initially 1 set of 10–15 repetitions should be completed. The ADA has suggested that high intensity resistance exercise may be performed by young individuals without longstanding diabetes, and that high repetitions using light weights may be performed by nearly all people with type 2 diabetes *(53)* . A reasonable recommendation is that resistance exercise should be performed at a moderate intensity (50–70% of 1-RM), by the majority of type 2 diabetic patients after appropriate medical screening and clearance by a medical professional (Grade: 1B). It is recommended that resistance exercise include 8–12 exercises using major muscle groups, and that 2–3 sets of 8–15 repetitions be completed (Grade: 1B). Patients with mild to moderate complications such as cardiovascular disease, nephropathy, or peripheral vascular disease may benefit from resistance exercise training. However, this should only be performed under the strict supervision and discretion of a health care provider and according to those guidelines set forth by the ACSM.

### Resistance Exercise Frequency

In agreement with the recommendations set for by the ACSM *(55)*, it is recommended that resistance exercise be performed at least 3 times per week, on nonconsecutive days (Grade 1B).

## *Exercise Duration*

The ACSM recommends that exercise begin with 10 min and progress to 30 min per session *(55)*. When exercise sessions are of short duration (i.e., 10 min) the patient should perform multiple sessions within the day to obtain metabolic benefits *(1)* (Grade: 1C+). In individuals who are exercising at lower intensities (i.e., walking programs), it is recommended that the long-term goal for exercise duration be 1 h, to obtain optimal improvements in insulin action and glycemic control (Grade: 1B). For those individuals combining aerobic and resistance exercise, an exercise duration of 1 hour also may be necessary to obtain the desired benefits from both types of exercise (Grade: 2A).

## *Exercise Mode and Setting*

Clearly, the exercise chosen should be one that interests the patient to enhance adherence. It is recommended that, to improve insulin sensitivity and glycemic control, aerobic exercise should include major muscle groups, and involve nonweight bearing or low impact exercise (i.e., walking, stationary cycling and/or swimming) (Grade: 1B). When weight-bearing activities are included, proper foot care is necessary, including frequent examination of feet for lesions caused by this type of activity. In agreement with the ACSM and ADA *(53,55)*, resistance exercise training using major muscle groups, is recommended for individuals who have been medically cleared to perform this type of exercise (Grade: 1B). In addition, to obtain maximal insulin action and glycemic control enhancement, exercise training should combine both aerobic and resistance exercise, either on separate days, or during the same exercise session for those individuals with sufficient exercise tolerance (Grade: 1B). For safety and to enhance adherence, exercise should be performed in a supervised setting that is easily accessible to the patient (Grade: 1C).

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# 10 Type 2 Diabetes Mellitus: An Evidence-Based Approach to Practical Management

*Noninsulin Pharmacological Therapies*

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***CONTENTS***



**Summary**

This chapter reviews all available noninsulin hypoglycemic therapies and aims to provide a succinct, evidence-based reference for use of these agents in clinical practice. The cornerstone of type 2 diabetes (DM) treatment is dietary lifestyle modifications, exercise, and weight management. Though these measures should be part of every treatment regimen, the addition of pharmacologic treatment should be implemented soon after diagnosis if blood glucose control is not achieved. Early intervention with achievement of normoglycemia reduces long term complications and has the potential to slow progression of the disease. Combination therapy addressing the different pathophysiological pathways responsible for the development of type 2 diabetes represents a physiological approach to treatment, and usually yields higher rates of success. Failure of oral hypoglycemic agents occurs over time in the majority of patients, and insulin therapy is eventually needed.

**Key Words:** Type 2 diabetes mellitus; insulin sensitizers; insulin secretagogues; incretin mimetics; amylin; alpha-glucosidase inhibitors; pharmacologic treatment of diabetes.

## INTRODUCTION

In the last few years the pharmacological repertoire for treatment of type 2 diabetes mellitus (DM) has seen a tremendous explosion. There have not only been new additions to the older classes of medications but several new classes of drugs have been developed. Although the availability of these options offers more flexibility and allows treatment to be better tailored to the individual patient's needs, it can also be challenging to keep up with so much new information and to translate it into clinical practice. This chapter reviews all available noninsulin hypoglycemic therapies and aims to provide a succinct, evidence-based reference for use of these agents in clinical practice.

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Trends in the use of various treatment regimens for type 2 diabetes have changed *(1)*. In NHANES III (1988–1994), 27.4% of the diabetic patients were treated with lifestyle modifications alone, and 47.5% were taking at least 1 oral hypoglycemic agent. In NHANES 1999–2000, the percentage of patients not treated with any modality other than lifestyle modification dropped to 20.2%, and 63.5% were taking at least 1 oral hypoglycemic agent. Despite the increase in the use of pharmacological treatment, overall glycemic control has not improved; in fact, it seems to have worsened. This supports the importance of education of patients and their physicians in the adequate use of the available armamentarium.

## CLASSIFICATION

Oral hypoglycemic agents have been classically divided in 2 large groups based on their mechanism of action: insulin secretagogues and insulin sensitizers. In recent years, new classes have been developed to address other pathophysiologic mechanisms involved in type 2 diabetes: incretin mimetics and amylin analogues.

## INSULIN SENSITIZERS

One of the causal pathways for type 2 diabetes is insulin resistance; the majority of patients with type 2 DM have significant insulin resistance *(2,3)*. Because insulin sensitizers do not promote insulin secretion, efforts to improve glycemic control with these drugs depend on preserved beta cell function. Several population-based studies showed that insulin resistance alone has been associated with cardiovascular disease (CVD) *(4)*. Because CVD is the most important morbidity and mortality factor in patients with type 2 DM, reduction of insulin resistance and other therapies directed at reducing cardiovascular risk factors may be as important as management of hyperglycemia.

### *Biguanides*

#### Overview

The only biguanide currently used in the US is metformin. The first agent in this class, phenformin, was withdrawn from the market in the late 1970s owing to an unacceptably high risk of fatal lactic acidosis associated with its use. Metformin has been used for type 2 DM for several decades in Europe, and has been available since 1995 in the United States *(5)*. Its exact mechanism(s) of action are not clear, despite decades of clinical use. However, 2 theories have been postulated: decreased hepatic gluconeogenesis *(6,7)*, and an insulin sensitizing effect in the liver and skeletal muscle *(8–10)*. Studies have also shown that metformin can decrease fatty acid turnover, thus decreasing free fatty acid (FFA) levels *(11,12)*. A decrease in FFA level is thought to have a role in increasing glucose uptake by peripheral tissues, thus decreasing plasma glucose levels *(12)*.

Metformin is available in strengths of 500 mg, 850 mg, and 1,000 mg tablets, as extended release form in strengths of 500 mg, 750 mg, and 1,000 mg, and a liquid form with 500 mg of metformin per 5 mL. The recommended starting dose is 500 mg or 850 mg once daily on a full stomach, to prevent gastrointestinal side effects *(5)*. The dose should be increased slowly every 1 to 2 wk to the maximum effective dose is 2,000 mg per day *(13)*.

It can be given at any time during the day and is usually given in divided dose to prevent gastrointestinal side effects.

#### Efficacy

Metformin is typically initiated as monotherapy when dietary and exercise therapy fails *(5,14)*. Most placebo controlled trials have shown that metformin monotherapy improves HbA1c by 1 to 2% *(13,15,16)*. When compared with sulfonylureas in head to head trials, the effect on HbA1c is similar *(17,18)*.

In the United Kingdom Prospective Diabetes Study (UKPDS), metformin reduced macrovascular complications among overweight (>120% ideal body weight) patients with type 2 DM. In the conventionally treated overweight patients, 62% of the total mortality rate was owing to CVD, whereas the metformin treated group had a 36% reduction of all cause mortality and 39% reduction in the incidence of myocardial infarction. The sulfonylurea and

insulin treatment groups did not demonstrate significant cardiovascular event reduction despite similar glycemic control *(19)*.

Metformin is associated with some weight loss or no weight gain *(5,6,19–21)*. It has also been shown to reduce the weight gain associated with other hypoglycemic agents *(22)*.

#### Safety

The most common side effect associated with metformin use is gastrointestinal disturbance (5–20%), including abdominal discomfort, nausea, and diarrhea *(5,23)*. These can be minimized or prevented by administering it on full stomach, initiating this agent at very low doses and titrating upward slowly. Using an extended release preparation may further prevent gastrointestinal symptoms. Other common side effects include: metallic taste and decreased vitamin B12 absorption. Lactic acidosis is a very rare (up to 0.4 cases per 10,000 treatment years) *(24)*, life threatening condition (mortality is about 30%), that may occur at increased frequency in patients using metformin *(5,24)*. This complication is more common in patients with preexistent risk factors for lactic acidosis (i.e., renal insufficiency, age over 80, alcoholism), raising the question of whether metformin is primarily responsible. However, the benefit of metformin use should be carefully weighed against the risks in these groups. Proper patient selection will eliminate metformin associated lactic acidosis *(25)*.

Metformin is contraindicated in patients with renal insufficiency (serum creatinine >1.4 mg/dL in women and >1.5 mg/dL in men), congestive heart failure requiring treatment, previous history of lactic or metabolic acidosis, impaired hepatic function, alcoholism, states with reduced peripheral circulation (respiratory insufficiency, cardiovascular collapse), or severe infections *(26)*. It should be used with care in the elderly, and the risk probably outweighs the benefit in patients over the age of 80 *(27)*. Metformin should be temporarily discontinued at the time of, or before, any radiologic study using iodinated contrast media, and for 48 h subsequent to the procedure; it should be reinstituted only after renal function has been re-evaluated and found to be normal.

#### Conclusions

Metformin is an effective insulin sensitizer, and with proper patient selection and a slow titration schedule, it is safe and well tolerated. It can be used as monotherapy or in combination with other hypoglycemic agents to achieve glycemic control in patients with type 2 DM. Metformin has also been shown to reduce cardiovascular morbidity and overall mortality in overweight patients.

### *Thiazolidinediones (PPARγ agonists)*

#### Overview

This class of oral hypoglycemic agents debuted on the US market in 1997 with the release of troglitazone. This agent was an effective insulin sensitizer and was also shown to decrease significantly the rate of conversion to type 2 DM in high risk patients *(28)*. However, troglitazone was removed from the market in 1999 owing to the rare development of an idiosyncratic hepatocellular injury *(29–31)*. In the same year, the FDA approved both pioglitazone and rosiglitazone for treatment of type 2 DM. Thus far they have not demonstrated significant hepatotoxicity *(32,33)*.

Thiazolidinediones (TZDs) are selective ligands of the nuclear transcription factor peroxisome proliferators activated receptor γ (PPARγ) *(34–36)*. The PPARs, which include a group of 3 nuclear receptor isoforms, PPARα, PPARγ, and PPARσ, are a subfamily of ligand activated transcription factors (includes the retinoic acid receptor, the steroid hormone receptors, and thyroid hormone receptors) *(37)*. The PPARs regulate gene expression in response to ligand binding *(36,38)*. PPARγ is expressed primarily in adipose tissue (>10-fold higher than in muscle) but is also found in pancreatic beta cells, vascular endothelial cells, colon epithelium, skeletal muscle, and macrophages *(36)*. The exact cellular mechanisms of action of TZDs on the PPARγ receptor are controversial. TZDs activate PPARγ receptors and form a heterodimer with the retinoid X receptor (RXR). This heterodimer product recognizes specific DNA elements called PPAR response elements (PPRE) in the promoter region of target genes, which may coactivate or coinhibit the target genes *(36,38)*. These protein products 1) regulate lipid metabolism to decrease free fatty acids, reduce lipolysis, and increase adipocyte differentiation *(39–41)*, 2) control cellular energy homeostasis *(42,43)*, 3) improve insulin sensitivity by increasing plasma levels of adipocyte related

complement protein 30 (ACRP30), also known as adiponectin *(44,45)*, and 4) inhibitis tissue necrotic factor-α (TNFα) *(46,47)*. Overall, these actions result in increasing insulin stimulated glucose uptake by skeletal muscle *(38,48)*.

Rosiglitazone is available in 2mg, 4mg, and 8mg tablets, and pioglitazone is available in 15 mg, 30 mg, and 45 mg tablets. Both are approved for monotherapy or in combination with sulfonylureas, metformin, sitagliptin, or insulin for patients with type 2 DM. The recommended starting dose for rosiglitazone is 2 mg daily and the maximum recommended dose is 8 mg daily. The starting dose for pioglitazone is 15 mg daily, and the maximum dose is 45 mg daily. Therapeutic efficacy increased with higher doses.

### Efficacy

In placebo controlled trials, rosiglitazone 8mg daily and pioglitazone 45 mg daily showed about 1.5% improvement in HbA1c after 6 mo of treatment *(50,51)*. The maximum hypoglycemic efficacy of both rosiglitazone and pioglitazone occur 3 to 4 mo after initiation of treatment *(49)*. The exact mechanism for this delay in maximal therapeutic effect is not known. The glycemic lowering effect of these agents is slightly less than that reported with sulfonylureas *(50,51)* or metformin *(13,15,16)*, yet the durability of glycemic control is superior *(52)*. The ADOPT study *(52)* showed that the durability of monotherapy with rosiglitazone was superior to monotherapy with metformin or glyburide over a 4 yr period.

In addition to improving insulin sensitivity, TZDs have the following effects: 1) improve dyslipidemia by increasing plasma HDL and, to some extent, lower triglycerides *(53)*, 2) reduce systolic and diastolic blood pressure by up to 5 mmHg *(54)*, 3) improve endothelial function by increasing endothelial nitric oxide levels *(55,56)*, 4) decrease inflammatory markers such TNFα, C-reactive protein, soluble CD40 ligand, and plasma monocyte chemoattractant protein-1 (MCP-1) *(46,47,57,58)*, and 5) enhance fibrinolysis by decreasing plasma plasminogen activator inhibitor-1 (PAI-1) *(59,60)*. All of these actions are beneficial from a cardiovascular standpoint and should translate into an improved risk of mortality and cardiovascular disease-associated morbidity. The Prospective Pioglitazone Clinical Trial In Macro Vascular Events study (PROactive study) evaluated the effect of pioglitazone as a secondary cardiovascular prevention agent in patients with type 2 DM, and showed some improvement in secondary end points, including all cause mortality, nonfatal myocardial infarction, and stroke *(61)*. Of note, the primary endpoint of the study, a composite of all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle, did not reach statistical significance. Patients treated with pioglitazone had more heart failure-related hospital admissions *(61)*.

TZDs can be used effectively in combination with metformin and/or insulin secretagogue agents. Several such combinations are now available (e.g., rosiglitazone/metformin, pioglitazone/metformin, rosiglitazone/glimepiride), offering the advantage of both agents while improving patient compliance and cost.

### Safety

TZDs are contraindicated in patients with class III or IV heart failure (CHF), pedal or pulmonary edema, significant anemia, or significant hepatic dysfunction *(62)*. Common adverse events with both agents are fluid retention causing peripheral edema, CHF, and weight gain *(49,63,64)*. Weight gain is likely owing to multiple factors, including peripheral edema and an increase in subcutaneous adipose tissue. TZDs are thought to cause a redistribution of fat from the visceral tissues to the subcutaneous tissues *(65,66)*. The incidence of pedal edema with TZD monotherapy ranges from 3 to 5%, and is greater when used in combination with metformin, sulfonylureas, or insulin *(49)*. The exact mechanism of fluid retention and CHF with TZD use is not known, but there are some hypotheses implicating a reduction of renal sodium excretion leading to free water retention *(67)*, or alteration in endothelial permeability *(68)*.

In 2003, the American Heart Association (AHA) and the American Diabetes Association (ADA) published a consensus guideline regarding TZD use, management of fluid retention, and CHF *(63)*. Before use, they recommend obtaining from each patient: 1) detailed cardiac disease history, 2) history of medication use associated with fluid retention (e.g. vasodilator, nonsteroidal anti-inflammatory drugs (NSAIDS), calcium channel blocker), 3) work up of preexisting edema, 4) baseline review of systems, including shortness of breath, and 5) recent ECG to rule out any silent myocardial infarction or left ventricular hypertrophy. The patient should be instructed

to report any new weight gain over 3 kg, acute onset of pedal edema, or shortness of breath *(63)*. For patients with class I or II NYHA CHF, TZDs may be used with caution, and initial TZDs dose should be lower (e.g., rosiglitazone 2 mg daily or pioglitazone 15 mg daily) and increased gradually over a period of several months *(63)*. AHA/ADA recommendations for monitoring patients on TZDs include: 1) if edema develops within the first few months of TZD therapy, the physician should determine whether CHF is present. A noninvasive cardiac evaluation, including an ECG and echocardiogram, should be performed. An exercise tolerance test or imaging stress test (echo or perfusion) may be indicated if any of the symptoms are thought to be of ischemic origin. 2) if edema occurs without evidence of CHF, rule out other causes of edema first (e.g., other medications such as NSAIDs, calcium channel blockers, nephrotic syndrome, venous insufficiency). A diuretic may be initiated or titrated for those patients who do not tolerate pedal edema. Effectiveness of diuretics on TZDs related edema may be variable. 3) if patients are diagnosed with or speculated to have CHF, even in the absence of previous left ventricular dysfunction, the physician should reconsider the use of TZDs *(63)*. The increased risk of CHF in patients with type 2 diabetes using TZDs has prompted the Food and Drug Administration (FDA) to mandate the addition of a black box warning to the package inserts of both pioglitazone and rosiglitazone.

In addition to the increased risk of CHF, this class has come under scrutiny for possibly increasing the risk of myocardial infarction and death owing to cardiovascular events. A published meta-analysis of 42 rosiglitazone trials showed an increase in the relative risk of myocardial infarction (OR = 1.43), and an increase in the relative risk of death caused by cardiovascular events (OR = 1.64) *(69)*. These findings prompted the FDA to reevaluate the safety data associated with the use of TZDs. As definitive trials assessing cardiovascular risk end-points are not available for rosiglitazone and acknowledging the limitations associated with available meta-analysis, the FDAs expert advisory committee recommended that rosiglitazone continue to be marketed *(70)*.The PROactive study with pioglitazone failed to show an increase in myocardial infarction, making it possible that either the conclusion of the meta-analysis is erroneous, or that there are differences in outcomes in term of cardiovascular events between the 2 thiazolidinediones. An open label prospective trial Rosiglitazone Evaluated for Cardiovascular Outcomes (RECORD trial) is underway and evaluates the effects of rosiglitazone on cardiovascular events *(71)*. These results should be available in 2009 and may provide more information about the long-term cardiovascular effects of rosiglitazone *(71)*.

#### Conclusions

TZDs are good insulin sensitizing agents. Until further information is available regarding their cardiovascular effects, patient should be carefully selected and counseled before therapy initiation. The relatively common occurrence of fluid retention and CHF should prompt close observation following therapy initiation, especially when they are used in combination with insulin.

### *Glitazars (dual PPARγ and α agonists)*

PPAR α regulates expression of various genes associated with lipid oxidation, mainly in liver, kidney, heart, skeletal muscle, and brown fat *(72)*, induces expression of the fatty acid transporter protein (FATP) and fatty acid translocase (FAT) *(73,74)*, and directly upregulates transcription of acetyl-CoA synthase *(40)*. Examples of PPAR α agonists are fibrates, such as gemfibrozil and fenofibrate. These agents decrease plasma triglyceride (TG) levels and cause a modest increase in HDL level. In the Veteran's Affairs High-density lipoprotein cholesterol Intervention Trial (VA-HIT trial), gemfibrozil therapy resulted in a significant reduction in the risk of major cardiovascular events in patients with coronary disease whose primary lipid abnormality was a low HDL cholesterol level. *(75)*. In theory, a dual PPAR α and γ agonist agent should be an ideal drug to treat type 2 DM with a dual mechanism of action: insulin sensitizer and improvement of dyslipidemia.

Combined PPAR α and γ agonists, called glitazars, are divided into 2 subgroups: thiazolidinedione variants (e.g., DRF-2189, KRP-297) and nonthiazolidinedione variants (e.g., muraglitazar = BMS-298585, tesaglitazar (GALIDA) = AZ-242 and ragaglitazar = NN-622) *(76)*. Currently no glitazars are FDA approved. A review of the pooled data from phase 2 and 3 clinical trials for muraglitazar showed an increase in the relative risk for the composite end point, including death, myocardial infarction, and stroke *(77)*. Ragaglitazar was found to be associated with soft tissue neoplasm in rodents *(76)*, which halted further development. Safety issues, including cardiovascular risk assessment, need to be resolved before these agents are recommended for use in type 2 DM.

## INSULIN SECRETAGOGUES

### *Sulfonylureas*

#### Overview

Sulphonylureas are the oldest oral hypoglycemic drugs and remain the most frequently used in the United States, accounting for over one third of oral antidiabetic prescriptions *(78)*. The first generation agents (tolbutamide, acetohexamide, chlorpropamide, and tolazamide) have largely been replaced by the second generation sulphonylureas (glyburide, glipizide, glimepiride).

These agents stimulate the release of preformed insulin by binding to the ATP-sensitive potassium channels receptors (SUR subunit) on the pancreatic beta-cell surface, but do not directly stimulate insulin production. They may also have a peripheral effect on insulin sensitivity *(79,80)*. They are indicated in patients with type 2 diabetes, for use alone or in combination with other hypoglycemic agents or insulin. The combination of sulfonylureas with short-acting mealtime insulin has no physiologic basis and is not advisable owing to the increased risk of hypoglycemia.

The dosage regimen for the second generation agents is listed in Table 1. Once daily dosage is appropriate for all formulations, but glyburide and glipizide can also be given twice daily if needed. Populations at risk of hypoglycemia (elderly, renal or hepatic insufficiency) should be started at even lower doses, and then slowly titrated upward as tolerated. Sulfonylureas are effective within 24 h of initiation and reach a steady state after 1–2 wk of therapy. Thus, dose adjustments should be done no sooner than every 1–2 wk. Dose ranging studies have noted that the maximum effective dose for these agents are less than the maximum daily dose listed on the package insert by the manufacturer. The maximum effective dose for each agent is shown in the Table 1.

#### Efficacy

The glucose lowering effect of sulfonylureas depends on the preexistent blood glucose level *(81,82)*. A decrease of up to 2% in the HbA1c is expected *(81,82)*. Previous studies have shown that failure of monotherapy with sulfonylureas occurs at a rate of 5–7% a year, and that after 10 yrs of treatment most patients require additional treatment to achieve glycemic control *(82,83)*. All agents in this class seem to have equal effect at equivalent doses *(81,82,84)*.

The combination of an agent with insulin secretagogue action and an agent that reduces insulin resistance represents a physiologic approach to the treatment of type 2 DM. Several such combinations agents are now currently on the market: glimepride/metformin, glyburide/metformin, glimepride/rosiglitazone. These combine the effectiveness of both agents *(85,86)*, and are thought to improve compliance and reduce the cost of treatment.

The effect of sulfonylureas on lipid profile components is slightly positive or neutral *(82,87)*. These agents are known to predispose to weight gain, with an average weight gain of 2–4 kg observed.

#### Safety

The most common side effect associated with the use of sulfonylureas is hypoglycemia *(83)*. Elderly patients and those with liver or renal insufficiency are at increased risk. Use of agents with a longer half-life may further increase the risk of hypoglycemia, though this has not been proven in a head-to-head trial *(88)*.

**Table 1**
**Dosing of sulfonylureas**

| *Agent* | *Starting dose* | *Maximum daily dose* | *Maximum effective dose* |
|---|---|---|---|
| Glyburide | 2.5 mg/day | 20 mg/day | 10 mg/day *(40,41)* |
| Glipizide SR | 2.5 – 5 mg/day | 20 mg/day | 10 mg/day *(37–39)* |
| Glipizide | 2.5 – 5 mg/day | 40 mg/day | 20 mg/day |
| Glimepiride | 1 mg/day | 8 mg/day | 4 mg/day *(42)* |

The effect of sulfonylureas on the heart has been long debated *(89,90)*. The University Group Diabetes Program was first to report that patients using tolbutamide, a first generation sulfonylurea, were at higher risk of death following myocardial infarction *(91)*. Because sulfonylurea class agents exert their secretagogue action by closing the KATP channels in the pancreas, it is biologically plausible that these agents also bind to the KATP channels in the myocardium and adversely effect ischemic preconditioning. Large scale clinical trials failed to confirm the association of sulfonylurea use with worsened clinical outcomes *(51,92)*, yet several smaller experimental studies showed that glyburide blocks the protective effect of ischemic preconditioning *(93–95)*. The current position of the American Diabetes Association, following review of the existent literature, is that there is no evidence that drugs from this class would worsen cardiac ischemia. The newer sulfonylurea agents (i.e., glimepiride) have lower affinity for the myocardial KATP channels and have not been implicated in this controversy. Given the comparable efficacy and safety, the use of these newer agents may be preferable, especially in patients at high risk for ischemic heart disease.

Some authors believe that the constant beta-cell stimulation that occurs with sulfonylureas might lead to "exhaustion" and apoptosis, but this has not been proven *in vivo (96)*.

#### Conclusion

The sulfonylurea agents are the most potent hypoglycemic agents, but failure of these agents occurs in most patients within 5–10 yr of treatment. Their most common side effect is hypoglycemia.

### *Nonsulfonylurea Secretagogues*

#### Overview

Two agents comprise this class: repaglinide and nateglinide. They are hypoglycemic agents approved for monotherapy or in combination with other oral hypoglycemic agents (except sulfonylureas) for treatment of type 2 diabetic patients. They have a similar mechanism of action to the sulfonylurea drugs; nonsulfonylurea secretagogues bind to the SUR receptor and inhibit the ATP-dependent K-channels on the beta-cells, thus stimulating insulin secretion *(97,98)*. In vitro studies suggest that nateglinide inhibits $K_{ATP}$ channels more rapidly, and with a shorter duration of action, than glibenclamide or glimepiride, and has a greater degree of specificity for SUR1 versus SUR2 *(97,99)*.

Nateglinide is available in 60 and 120 mg tablets. The usual dose is 120 mg with each major meal. Repaglinide is available in 0.5, 1, and 2 mg tablets. The starting dose is 0.5mg before each meal, with a maximum of 16 mg/day. They have a half life of 1–1.5 h *(100)*.

#### Efficacy

The major effect of these drugs is the reduction of postprandial plasma glucose, with a smaller effect on fasting plasma glucose and HbA1c reduction. In 12- and 24-wk trials, nateglinide showed a HbA1c lowering effect of 0.7 and 0.5% *(101,102)*. In head to head trials of repaglinide and nateglinide, repaglinide showed a greater HbA1c reduction *(103,104)*. When nateglinide was compared to glyburide, a similar overall glycemic effect was observed after 105 wk of therapy *(105)*.

The effect of the nonsulfonylurea secretagogues on diabetes related morbidity and mortality has only been evaluated in short term studies, with surrogate end-points *(106–108)*. These have shown a possible beneficial effect of these agents on carotid atherosclerosis, brachial artery reactivity, or postprandial rise in triglyceride levels.

In a small, 16-wk randomized study, nateglinide showed a positive effect on nonalcoholic steatohepatitis (NASH) *(109)*. The use of nonsulfonylurea secretagogues in patients with prediabetes is also being studied *(110)*, with results expected after 2007.

The combination of a nonsulfonylurea insulin secretagogue with an insulin sensitizing agent represents a rational treatment approach. The addition of these agents to metformin or a thiazolidinedione further lowers the HbA1c, allowing more patients to reach current treatment guideline targets *(111,112)*.

### Safety

The biggest benefit of the nonsulfonylurea secretagogues over the sulfonylurea agents is the short acting profile and ability to time the administration with the major meals, thus reducing the risk of hypoglycemia *(105)*. Weight gain of 2–3 kg has been reported in clinical studies, but this is slightly less than that seen with sulfonylureas *(101,102,112)*. They are better tolerated than sulfonylureas by patients with chronic kidney disease *(103)*.

### Conclusion

Nonsulfonylurea secretagogues are short acting insulin secretagogues that mainly lower postprandial glucose levels, with a modest effect on HbA1c values. They have a low hypoglycemia rate and are well tolerated by patients at high risk of hypoglycemia, especially patients with chronic kidney disease.

## ALPHA-GLUCOSIDASE INHIBITORS

### *Overview*

The first agent in this class, acarbose, was approved by the FDA in September 1995. Miglitol is another agent in this class available in the US, whereas voglibose and emiglitate are available overseas.

Alpha-glucosidase inhibitors are indicated for the treatment of type 2 diabetes mellitus alone or in combination with other antidiabetic agents. They reversibly inhibit the enzyme alpha-glucoside hydrolase, situated in the brush border of the small intestine. A delay in the absorption of complex carbohydrates occurs, leading to decreased postprandial peak glucose (and insulin) levels.

Acarbose and miglitol are supplied as tablets of 25 mg, 50 mg, and 100 mg. The starting dose is 25 mg before each meal, and can be increased to maximum of 100 mg TID. More than half of an acarbose dose is excreted in feces, whereas miglitol is mainly excreted in the urine. The half life of these drugs is 2 h.

### *Efficacy*

Monotherapy with alpha-glucosidase inhibitors in type 2 diabetes was systematically reviewed in 2005 *(113)*. Based on the analysis of 41 randomized trials, after an average of 24 wk of therapy, acarbose lowers HbA1c by 0.8% compared with placebo. It also reduces significantly fasting plasma glucose and postload blood glucose levels. Interestingly, the effect of acarbose on HbA1c is not dose dependent, and at doses above 50 mg TID, there is no additional improvement in HbA1c, although the occurrence of side effects increases. When compared with sulfonylureas, acarbose has less hypoglycemic effect and more side effects, but fasting and postload insulin levels are lower *(113)*. In a randomized, 26-wk, open-label study, acarbose had a smaller hypoglycemic effect than pioglitazone *(114)*. Alpha-glucosidase inhibitors have no effect on weight and lipid profile *(113)*.

Addition of acarbose to an insulin containing regimen reduces the acute glycemic response in patients with type 2 DM *(115,116)*. The combination of miglitol and metformin is beneficial for overall glycemic control, fasting plasma glucose, and postprandial glycemic excursion *(117,118)*.

No randomized controlled trials evaluating the effect of alpha-glucosidase inhibitors on diabetes related morbidity or mortality endpoints exist. The STOP-NIDDM study, evaluating the rate of progression to diabetes in patients with IGT treated with acarbose versus placebo, had as a secondary endpoint the occurrence of cardiovascular events. The authors reported a decrease in the composite endpoint, including coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease *(119)*.

Acarbose in patients with IGT slows the conversion rate to diabetes *(120)*. Use of alpha-glucosidase inhibitors in women with PCOS has favorable results on hormonal measurements, hirsutism, and menstrual pattern *(121,122)*. The effect on fertility has not been assessed.

Successful use of these agents for idiopathic reactive hypoglycemia *(123)* and postgastrectomy dumping syndrome *(124)* has been reported.

### *Safety*

The most common side effects are of gastrointestinal origin, including bloating, diarrhea, flatus, nausea, abdominal pain. These effects are dose dependent. In fact, in the STOP-NIDDM study, 31% of the patients treated

with acarbose (versus 19% treated with placebo) discontinued treatment *(120)*. Alpha-glucosidase inhibitors do not cause hypoglycemia.

### *Conclusion*

Alpha-glucosidase inhibitors have a modest glucose lowering effect, a neutral effect on weight, and a commonly cause gastrointestinal side-effects. They can be used alone or in combination with other hypoglycemic agents for treatment of type 2 diabetes, as well as for prevention of diabetes in high-risk groups. Their low risk of systemic side-effects makes them desirable in patients who have contraindications or side-effects to other hypoglycemic classes.

## INCRETIN MIMETICS

Incretin hormones are gut hormones that increase insulin secretion after oral ingestion of carbohydrates *(125)*. The "incretin effect" is the augmented insulin secretion effect of an oral glucose load compared with an IV load *(125)*. The most important incretin hormones are glucose dependent insulinotropic polypeptide (GIP) and glucagon like peptide (GLP)-1 *(126)*. GIP is secreted by K-cells located in the upper part of the small intestine, and GLP-1 is released by L-cells distributed throughout the small and large intestines *(127,128)*.

### *GLP-1 Agonists*

#### Overview

GLP-1 is a more potent insulinotropic agent than GIP. It has several mechanisms through which it improves hyperglycemia: reduced glucagon secretion from α cells during hyperglycemia *(126,128)*, delayed gastric emptying in a dose related manner *(128,129)*, and increased satiety and decreased food intake through a direct action on the central nervous system or through negative feedback from a distended stomach *(128)*. Some animal models have shown that GLP-1 may delay or reverse apoptosis and cause proliferation of β cells *(128,130,131)*. A characteristic difference between GLP-1 and other secretagogues like sulfonylureas is that GLP-1 does not cause hypoglycemia *(126,128)*.

GLP-1 is secreted by the intestinal L cells and is rapidly metabolized by the plasma enzyme dipeptidyl peptidase IV (DPP IV) *(126,128,132)*. DPP IV inhibitors enhance the incretin effect of GLP-1 by preventing its degradation *(73)*.

The FDA approved exenatide in April 2005. Exenatide is a GLP-1 agonist, which has been isolated from the salivary gland of the Gila monster, and is not easily metabolized by DPP IV, thus enhancing its duration of action *(126,128)*. An albumin bound GLP-1 derivative (Liraglutide-NN2211) is undergoing phase 3 trials and is pending approval.

Exenatide is approved as adjunctive therapy to improve glycemic control in patients with uncontrolled type 2 DM who are already using metformin and/or sulfonylureas *(133)*. The initial recommended dose is 5 mcg subcutaneously twice daily, which can be increased to 10 mcg subcutaneously twice daily if the patient tolerates the initial dose for 1 mo *(133)*. If used in combination with a sulfonylurea, the dose of the sulfonylurea agent may need to be decreased to reduce the risk of hypoglycemia *(133)*.

#### Efficacy

Several clinical trials have shown that exenatide, when combined with metformin and/or sufonylureas, improve HbA1c levels by 1% and is associated with dose dependent weight loss (−2.8 kg [10mcg], −1.6 kg [5mcg]) *(134,135)*.

#### Safety

The most common adverse events of exenatide include nausea (44%), diarrhea (13%), vomiting (13%), dizziness (9%), and headache (9%) *(133)*. Few hypoglycemic incidents have been reported among patients, and only with concomitant treatment with sulfonylureas *(135)*. No other significant adverse events have been reported.

Hypoglycemic precautions should be taken when exenatide is used in combination with insulin, thiazolidinediones, D-phenylalanine derivatives, nonsulfonylurea secretagogues, or alpha-glucosidase inhibitors, as well as

in end-stage renal disease or severe renal impairment (creatinine clearance < 30 mL/min). It should also be used cautiously if severe gastrointestinal disease, including gastroparesis, as it may cause further delay in gastric emptying *(133)*.

#### Conclusion

Exenatide is the first agent in the incretin mimetic class. It has a similar hypoglycemic effect to other known antidiabetic agents, but it has the added advantage of weight loss and it may also have a role in beta cell proliferation along with preventing beta cell apoptosis. It is administered subcutaneously and has a relatively common occurrence of nausea that may limit its tolerability and compliance.

### *DPP IV Inhibitors*

#### Overview

In animal models, DPP IV inhibitors have been shown to enhance the incretin effect of both GLP-1 and GIP *(76,136)*. When DPP IV inhibitors are compared to a GLP-1 agonist, the DPP IV inhibitors have no effect on weight and results in less improvement in glycemic control *(76)*. However, a benefit of DPP IV inhibitors over GLP-1 agonists is their oral formulation *(76)*.

Sitagliptin is the first agent in this class approved by the FDA. Vildagliptin and saxagliptin are other oral DPP IV inhibitors undergoing phase 3 trials.

Sitagliptin is a highly selective DPP IV inhibitor *(137)*. It is approved for use as mono-therapy or in combination with metformin or TZDs to improve glycemic control in patients with type 2 DM. The recommended dose is 100 mg orally once a day, or if sitagliptin/metformin combination is used, dosing should be individualized depending on patient's current regimen (from 50mg/500mg orally twice a day to maximum of 100mg/2000mg a day) *(138)*.

#### Efficacy

Several clinical trials have shown that sitagliptin improve HbA1c levels by up to 1% *(139–144)*. In a 52 wk randomized, placebo controlled, clinical trial in 107 patients with type 2 DM on stable dosage of metformin, a mild improvement of HbA1c ($-0.6 \pm 0.1\%$) occurred in the DPP IV inhibitor group (LAF237, vildagliptin; 50mg daily) *(145)*. Other prospective clinical trials showed improvement in HbA1c of up to 1% with vildagliptin *(146–151)*.

#### Safety

The adverse effects of sitagliptin include a small increase in hypoglycemia events (1.2 % for sitagliptin compared to 0.9% for placebo), gastrointestinal adverse effects such as abdominal pain (2.3% for sitagliptin compared to 2.1% for placebo), diarrhea (3% for sitagliptin compared to 2.3% for placebo) and nausea (1.4% for sitagliptin compared to 0.6% for placebo) *(138)*. Other rare adverse effects included pruritus, dizziness, headache, and diaphoresis *(76)*. More studies are needed to further evaluate the side effects of DPP IV inhibitors, because they also have multiple other actions, including cleavage of neuropeptide Y, endomorphin, peptide YY, growth hormone releasing hormone, and other regulatory hormones *(128)*.

#### Conclusion

Sitagliptin has similar effects as GLP-1 agonists except for the weight loss. DPP IV inhibitors are oral formulations, which confer an advantage over the GLP-1 agonist class which are administered subcutaneously.

## AMYLIN AGONIST

### *Overview*

Pramlintide (Symlin) was approved by the FDA in March 2005 as a hypoglycemic agent for use in patients with type 1 or type 2 diabetes in conjunction with mealtime insulin *(152)*. In patients with type 2 diabetes, it is indicated as an adjunct therapy to mealtime short-acting insulin when adequate insulin therapy fails to achieve adequate glucose control, with or without a concurrent sulfonylurea agent and/or metformin *(152)*.

Pramlintide is a synthetic analogue of the naturally occurring hormone, amylin. Amylin is cosecreted with insulin by the pancreatic beta-cells, and its levels closely parallel those of insulin in healthy individuals as well as in patients with diabetes, rising 2–3-fold after ingestion of a mixed meal *(153)*.

The following mechanisms of action have been demonstrated for pramlintide: 1) delay in gastric emptying by approx 3 h *(154)*, thus decreasing the postprandial glucose rise; the net absorption of nutrients is not affected; 2) increased satiety through a centrally acting mechanism; and 3) prevention of the abnormal postprandial rise of plasma glucagon seen in patients with type 2 diabetes *(155)*, resulting in a blunted postprandial blood glucose rise, although glucagon release is not impaired during times of hypoglycemia *(152)*.

Pramlintide reaches peak concentration in 20 min, and has a half life of 50 min *(135)*. It is excreted by the kidneys, but no dose adjustments are required for creatinine clearance levels as low as 20 mL/min. It has not been evaluated in dialysis, pediatric, or geriatric patients, and the pregnancy rating is C. Pramlintide decreases the rate of absorption of other coadministered drugs owing to the delayed gastric emptying, but the peak concentration of these drugs is not altered.

The starting dose for patients with type 2 DM is 60 mcg per injection, up to 3 times a day. The dose can be increased every 3–7 d if no significant nausea occurs. The recommended dose is 120 mcg per injection up to 3 times daily. It should be injected subcutaneously in the thigh or abdomen, just before a meal *(156)*. It cannot be mixed with any insulin preparation in same syringe.

### *Efficacy*

In a 52-wk randomized, placebo controlled, trial of 656 patients with type 2 DM, using concomitant meal-time insulin treatment alone, or in combination with, sulfonylurea or metformin, the average HbA1c decreased by 0.62% in the group treated with 120 mcg BID of pramlintide (compared with −0.2% in the placebo group) *(157)*. The effect of pramlintide on weight was evaluated in a post hoc analysis of pooled data from 2 long term studies and included only patients with a BMI > 25 (n = 254 on pramlintide 120 mcg twice daily, n = 244 on placebo). After 6 mo of treatment, the treatment group lost 1.8 kg more than the placebo group. The greatest reduction was seen in patients with a BMI > 40 (−3.2 kg) and those concomitantly treated with metformin (−2.5 kg) *(158)*. The mechanism of weight loss is thought to be through a primary satiogenic effect, independent of other anorexigenic gut peptides *(159)*, and seems to be unrelated to the occurrence of nausea.

There is currently no information on diabetes-related morbidity or mortality outcomes in patients treated with pramlintide.

### *Safety*

Currently no data exist regarding the efficacy or safety of this agent beyond 3 yr of treatment. Owing to the possibility of severe hypoglycemic reactions following pramlintide injection, it is not indicated in patients with hypoglycemia unawareness. It is recommended that the mealtime insulin dose be decreased by 50% when starting this agent *(152)*. Other common adverse reactions are nausea, vomiting, and dyspepsia *(160)*. Pramlintide should not be used in combination with alpha-glucosidase inhibitors or any other agents that inhibit gastric emptying *(152)*.

### *Conclusion*

Pramlintide is a new agent indicated for the occasional patient who cannot achieve good postprandial glucose control despite adequate insulin therapy. When considering the addition of this drug to a current insulin regimen, one needs to balance its modest hypoglycemic action and the added benefit of weight loss with the common occurrence of nausea and the less common, but serious, occurrence of life threatening hypoglycemia. Proper patient selection is important, as the addition of this agent increases significantly the number of daily injections. Only very motivated and compliant patients should be selected. The price per month is in excess of $300, excluding syringes (Table 2).

Table 2
**Noninsulin pharmacological therapies for type 2 diabetes mellitus: available formulations, cost, HbA1c lowering effect, pregnancy category**

| *Agent* | *How Supplied* | *Generic** | *Price*** | *Reduction in HbA1c* | Pregnancy Category |
|---|---|---|---|---|---|
| metformin | 500, 850, 1000 | Y | 0.48 | 1.0 – 2.0 | B |
| metformin SR | 500, 750 | Y | 0.98 | 1.0 – 2.0 | B |
| pioglitazone | 15, 30, 45 | N | 5.95 | 1.5 | C |
| rosiglitazone | 2, 4, 8 | N | 5.99 | 1.5 | C |
| glyburide | 1.25, 2.5, 5 | Y | 0.2 | 1.0 – 2.0 | C |
| micronized glyburide | 1.5, 3, 4.5, 6 | Y | 0.58 | 1.0 – 2.0 | B |
| glipizide | 5, 10 | Y | 0.12 | 1.0 – 2.0 | C |
| glipizide SR | 2.5, 5, 10 | Y | 0.66 | 1.5–1.8 | C |
| glimepiride | 1, 2, 3, 4, 6, 8 | Y | 0.47 (4 mg) | 1.0 – 2.0 | C |
| nateglinide | 60, 120 | N | 1.36 | 0.5 – 1.0 | C |
| repaglinide | 0.5, 1, 2 | N | 1.27 | 0.5 – 1.0 | C |
| acarbose | 25, 50, 100 | N | 1.01 | 0.8 | B |
| miglitol | 25, 50, 100 | N | 0.95 | 0.8 | B |
| exenatide | 250 mcg/ml as 1.2 and 2.4 ml | N | 225.53 | 1.0 | C |
| sitagliptin | 100 | N | 5.46 | 0.7 | B |
| pramlintide | 0.6 mg/ml as 5 ml | N | 115.30 | 0.6 | C |

* As of 08/23/2007

** Price source www.drugstore.com as of 08/23/2007, price indicated is for a unit of the largest formulation available, unless otherwise indicated.

## CONCLUSIONS

Type 2 diabetes mellitus is a progressive disease, characterized by a decline in beta-cell function and subsequent worsening of glycemic control. Failure of oral hypoglycemic agents occurs over time in the majority of patients, and insulin therapy is eventually needed. The slope of beta-cell function decline can be improved if normal blood glucose levels are maintained. Thus, constant reassessment and adjustment of treatment is necessary to maintain normal or near-normal glycemia, and the use of early combination therapies with complementary mechanisms of action allows more patients to achieve and maintain these goals. Knowledge of the safety, efficacy, and cost profiles (Table 2) for each agent is necessary to devise and individualize the medical regimen, while accounting for patient preference and concomitant morbidities.

## GRADES OF RECOMMENDATION

| *Agent* | *Hypoglycemic effect* | *DM associated morbidity* | | *Mortality* |
|---|---|---|---|---|
| | | *Microvascular* | *Macrovascular* | |
| Metformin | 1A | 1B | 1B | 1B |
| Pioglitazone | 1A | NA | 2B | 2A |
| Rosiglitazone | 1A | NA | NA | NA |
| PPAR $\alpha$ & $\gamma$ | 1B | NA | NA | NA |
| Sulfonylureas | 1A | 1B | 2B | 2B |
| Meglitinides | 1A | 2B | 2B | NA |
| Acarbose | 1A | 2B | 2B | 2B |
| Exenatide | 1A | NA | NA | NA |
| Sitagliptin | 1B | NA | NA | NA |
| Pramlintide | 1A | NA | NA | NA |

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# 11 The Transition from Oral Agents to Combination Insulin/Oral Therapy

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***CONTENTS***



**Summary**

New therapeutic options and new information from clinical trials have improved treatment of type 2 diabetes, but also increased the complexity of clinical decisions by providing more options. This added complexity applies to the transition from oral therapies to insulin, as well as other aspects of treatment. Discussion of the transition from oral to insulin therapy is best started by reviewing the process of glycemic management of type 2 diabetes in general.

## PATHWAY FOR MANAGEMENT OF TYPE 2 DIABETES

### *Accepted Principles*

Several fundamental tactics for treatment of type 2 diabetes have become widely accepted *(1)*. One is the use of evidence-based methods wherever possible, emphasizing specific agents for which medical benefits have been established and adverse effects are well-described, with preference for simpler methods over more intricate ones. A second is individualization of treatment, adjusting dosage and timing of medications, and substituting one agent for another based on individualized clinical judgment rather than evidence from trials of large populations. Stated another way, appropriate individualization of treatment may, in some cases, require a less widely used method that may not be suited to all patients, rather than a standard treatment. A third principle is that a metabolic target should be established, and treatment adjusted to achieve this target. The most widely used target, backed by objective data, is an hemoglobin $A_{1c}$ (A1c) value of 7% or less, a laboratory value indicating glucose levels that are only slightly above normal. A final principle is sequential addition of therapies (rather than substitution of one for another) as the metabolic disorders underlying type 2 diabetes progress over time. Systematic use of 'combination therapy' is supported by evidence that multiple physiologic defects must be treated to reach desired levels of glycemic control *(2,3)*.

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### *Sequence of Treatments*

Of course, these principles must be applied over time. A patient with newly diagnosed diabetes is likely to respond well to almost any treatment and my require no pharmacologic therapy after increasing the frequency of physical activity and eating more wisely. When lifestyle efforts are found (or expected) to be insufficient, treatment with a single oral antihyperglycemic agent is usual, followed when necessary by additional oral therapy *(4)*. By 5–10 yr after diagnosis, insulin is generally needed *(5)*. In most cases oral agents are continued while insulin is started. Frequently, especially more than 15 yr after diagnosis of diabetes, multiple injections of insulin become necessary *(6)*. Some patients eventually need full "basal-bolus" insulin therapy, consisting of one or more injections of long-acting insulin together with an injection of more rapid-acting insulin with each meal. In general, simple, evidence-based treatments are effective in the first 10 yr after diagnosis, while later on treatment must be individualized.

## EVIDENCE-BASED MEDICATIONS FOR THE BASIC PATHWAY

Sulfonylureas, metformin, and insulin have been used for over 50 yr. Their desirable and unwanted effects are well known, and use of each has been shown to reduce many of the medical complications of diabetes *(7–9)*. Recently reported findings suggest that glyburide, one of the commonly used sulfonylureas, is less desirable than others (such as glipizide, gliclazide, or glimepiride) because it can impair protective vasodilatory responses to ischemia, causes more hypoglycemia, and may be associated with higher rates of mortality than with other secretatogues *(10–12)*. Less evidence supports the use of other (more recently available) oral agents, including rapid-acting secretagogues (repaglinide, nateglinide), alphaglucosidase inhibitors (acarbose, miglitol, voglibose), and thiazolidinediones (pioglitazone, rosiglitazone). Although recent reports suggest that acarbose or pioglitazone may reduce cardiovascular events, these benefits were shown in secondary analyses and therefore require confirmation *(13,14)*.

The best evidence for improvement of medical outcomes by oral therapies is that for metformin and sulfonylureas in the United Kingdom Prospective Diabetes Study (UKPDS) *(8,9)*. In part because of this evidence, pharmacotherapy for type 2 diabetes usually begins with either metformin or a sulfonylurea, and progresses to the use of the 2 together. The newer agents are (appropriately) used most often as alternatives to metformin or sulfonylureas in individual patients for whom they are judged to offer specific advantages. For example, patients not able to take metformin because they have impaired renal function, or suffer unacceptable gastrointestinal symptoms with even modest dosage, are appropriately prescribed a thiazolidinedione (TZD) instead. Similarly, patients with more prominent postprandial than fasting hyperglycemia may appropriately use an α-glucosidase inhibitor or a rapid acting secretagogue, rather than a sulfonylurea, to limit postprandial increments of glucose. Not surprisingly, in many studies of patients who are beginning insulin, most are taking 2 oral agents and nearly 70% are taking metformin and a sulfonylurea.

## TIMELY INTENSIFICATION OF THERAPY

Despite general approval of the idea that seeking the evidence-based 7% A1c target is desirable, community-based surveys show considerable resistance to acting on this principle *(15,16)*. Very often a second or third antihyperglycemic agent is not added until A1c has reached 9% or higher. Failure to intensify treatment may be partly due to lack of symptoms from hyperglycemia until fasting glycemia exceeds the renal threshold for glycosuria. However, both the physician and the patient may be reluctant to begin insulin therapy for other reasons. A patient's resistance to starting insulin may stem from fear of injections, concern about hypoglycemia, or distress about the symbolic meaning of insulin therapy, which is feared to signify impending amputation, blindness, or death. A physician's resistance to prescribing insulin may be owing to lack of time, concern about adverse effects including (but not limited to) hypoglycemia, and reluctance to manage a complex insulin regimen. Most of these fears and concerns turn out to be mainly unfounded, but the complexity of the process of initiating insulin remains a barrier to timely initiation of insulin. Therefore, development of simple, effective, and safe ways to progress beyond no-longer-successful therapy with 2 oral agents has attracted much attention in recent years.

## A THIRD AGENT BEFORE INSULIN?

A decade ago, there was little alternative to starting insulin when metformin plus a sulfonylurea no longer maintained acceptable glycemic control. Now there are 2 important alternatives, each with attractive features.

### *Adding a Thiazolidinedione*

The thiazolidinediones, pioglitazone and rosiglitazone, have mechanisms of action that are different from those of metformin and sulfonylureas *(4,17)*, and their antihyperglycemic effects are therefore fully additive. Carefully executed trials have shown that adding one of these agents to metformin and a sulfonylurea can reduce A1c by 1–2% (absolute value) from baseline *(18–21)*. As with other treatments, the greatest reductions are usually seen when initial glycemic control is very poor. One important study compared adding rosiglitazone with adding a single injection of a long-acting insulin analogue, insulin glargine in patients already taking metformin and sulfonylurea *(21)*. Both treatments achieved mean A1c values 7.1–7.2%. Although insulin caused more hypoglycemia, rosiglitazone caused more weight gain and peripheral edema. In a secondary analysis, patients starting with A1c 9.5% or higher obtained more reduction of A1c with insulin than with the TZD.

Adding a TZD to 2 oral agents is simple but has some limitations. One is lack of enough therapeutic power in many cases. As illustrated by the study just described, the 7% A1c target is not usually reached when A1c values are much above 8% when the TZD is added. In contrast, the therapeutic potential of insulin is greater, especially when multiple injections are used when needed. Another limitation lies in the side effects. Weight gain predictably occurs in some patients, due both to fluid retention and to an increase of peripheral fat mass. The gain in adiposity does not seem metabolically harmful *(22)*, but patients often object to it. In contrast, fluid retention may pose medical risks. Congestive heart failure can be precipitated in vulnerable patients, and this risk is probably underestimated by data from clinical trials from which patients with known heart disease have been excluded. Whether protection against other cardiovascular problems compensates for the effects of fluid retention caused by TZDs is still unknown.

The findings of the PROactive trial are pertinent to this question *(14)*. This study was designed to determine whether or not pioglitazone could reduce the occurrence of cardiovascular events or mortality, an effect that has been postulated from physiologic studies and animal experiments *(22)*. Five thousand two hundred thirty eight patients with type 2 diabetes and evidence of high cardiovascular risk were randomized to 45 mg pioglitazone or placebo. Persons with Class II through V heart failure were specifically excluded. About 25% were taking metformin and a sulfonylurea at entry, and another 34% were taking insulin together with one or more oral agents. After 3 yr follow-up, A1c was 0.5% lower with pioglitazone treatment than with placebo, and both blood pressure and lipid profiles improved slightly as well. The primary endpoint, a composite of various cardiovascular events, did not show a significant protective effect of pioglitazone. However, another analysis that had not been specified in the design paper showed a 16% reduction of events in a more restricted composite endpoint. Congestive heart failure was not included as a potential cardiovascular endpoint in the design, yet data collected for safety analysis showed about 50% more hospital admissions for this complication during pioglitazone treatment. In summary, this study showed a modest improvement of glycemic control with pioglitazone, but the primary analysis did not support the hypothesis that pioglitazone protects against cardiovascular events. Although a secondary analysis indicated some cardiovascular benefit, it is not clear that this derived from a unique mechanism separate from conventional risk factors *(23)*. In addition, the study confirmed that congestive heart failure may be precipitated by this therapy even in patients not previously known to have heart failure.

### *Adding Exenatide*

Studies of gastrointestinal peptide hormones that are involved in normal regulation of fuel physiology during meals have led to development of new pharmacologic treatments for type 2 diabetes *(24,25)*. The first of these to reach clinical use for patients no longer successful with oral therapies is exenatide, an agonist of the glucagon-like peptide-1 (GLP-1) receptor. Given twice daily by injection, it potentiates secretion of insulin and suppresses secretion of glucagon, slows gastric emptying, and promotes satiety. In type 2 diabetes, it modestly reduces fasting hyperglycemia but markedly suppresses postprandial increments and, in most cases, leads to weight-loss

as glycemic control improves. Three large trials have tested its use for patients taking metformin, a sulfonylurea, or both together *(26–28)*. A1c declined by about 1% from baseline levels between 8.2 and 8.6% in all these trials.

The main side effects of exenatide are nausea, which can lead to vomiting, especially at initiation of treatment, and mild to moderate hypoglycemia when it is added to a sulfonylurea. In the three 6 mo trials, the mean, placebo-adjusted weight-loss was 2.5, 1.0, and 0.9 kg, and weight-loss occurred even when nausea was absent. Uncontrolled long-term follow-up of patients in these trials suggests that, at least in some patients, weight-loss may continue for up to 1 ½ yr *(29)*.

Use of exenatide in this fashion has also been compared with addition of glargine to prior treatment with metformin and a sulfonylurea *(30)*. The mean baseline A1c of 8.2–8.3% was reduced after 6 mo in both treatment groups to 7.1–7.2%. Weight increased 1.8 kg with glargine but decreased 2.3 kg with exenatide. Overall rates of hypoglycemia were similar between the 2 treatments, but nausea, vomiting, and diarrhea were more common with exenatide.

The limitations of exenatide as a third agent are similar to those of the TZDs. No more than about 1% reduction of A1c can be expected, and patients starting treatment with A1c values well above 8% are not likely to reach the 7% target. Mild to moderate symptomatic side effects are common, and the potential long-term risks and benefits of this agent are unknown. However, the potential for modest weight loss accompanying improvement of glycemic control may prove to be medically important.

## HOW TO BEGIN INSULIN THERAPY?

Insulin therapy can be started in many ways, but 3 distinctive tactics have been widely used and well described in clinical studies. These 3 methods involve starting with 1) basal insulin once or twice daily; 2) prandial insulin 3 times daily; or 3) premixed insulin twice daily.

### *Basal Insulin*

The simplest method consists of adding a single injection of long-acting or intermediate-acting insulin *(31,32)*. Oral agents usually are continued, allowing lower dosages of insulin or better glycemic control. Studies document the ability of various insulins to supplement endogenous basal insulin levels, including bovine or human ultralente *(33)*, human NPH *(34,35)*, and human 70/30 (70% NPH/30% Regular) *(36)*, and the insulin analogue glargine *(37–39)*. A single injection is usually given at bedtime, but 70/30 insulin should be given before the evening meal, and glargine, with its long duration and relative lack of a peak effect, can be taken in the morning, before the evening meal, or at bedtime.

This method was well illustrated by the treat-to-target trial, which compared NPH and glargine added at bedtime to preceding treatment with one or 2 oral agents *(37)*. The trial enrolled 756 obese participants, 70% of whom had been taking metformin and a sulfonylurea. Oral therapies were continued as before, and the dosage of either insulin was systematically increased with the aim of suppressing the fasting plasma glucose concentration to 100 mg/dL. After 6 mo of treatment, mean fasting glucose levels were between 115 and 120 mg/dL, and mean A1c was reduced from 8.6% at baseline to just under 7% with either insulin (Fig. 1). Nearly 60% of those randomized reached the 7% A1c target. The 2 insulins were equally effective in improving glycemic control, but glargine caused significantly less hypoglycemia. The figure shows cumulative hypoglycemic events confirmed by a glucose value at or below 56 mg/dL, and use of glargine led to 41% fewer such events per patient-year. Hypoglycemia severe enough to require assistance by another person was very uncommon with both insulins.

Another important study (LANMET) confirmed that glycemic control can be maintained by this method at least up to 9 mo *(38)*. This study included 110 participants who added either glargine or NPH insulin at bedtime and systematically titrated the dosage while metformin was continued. Both groups achieved excellent mean fasting glucose levels (104 versus 107 mg/dL) and good A1c values (7.14 versus 7.16%).

The Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1c) trial examined how much the effectiveness of the aforementioned studies depended on the ways they were performed *(39)*. Of 7,605 patients studied, 47% had previously taken 2 oral agents and another 18% were taking metformin, a sulfonylurea, and a TZD. Most of the investigators were primary care physicians rather than diabetes specialists. All the patients were treated with glargine added to any prior oral therapies for 6 mo. Overall, mean A1c was reduced from

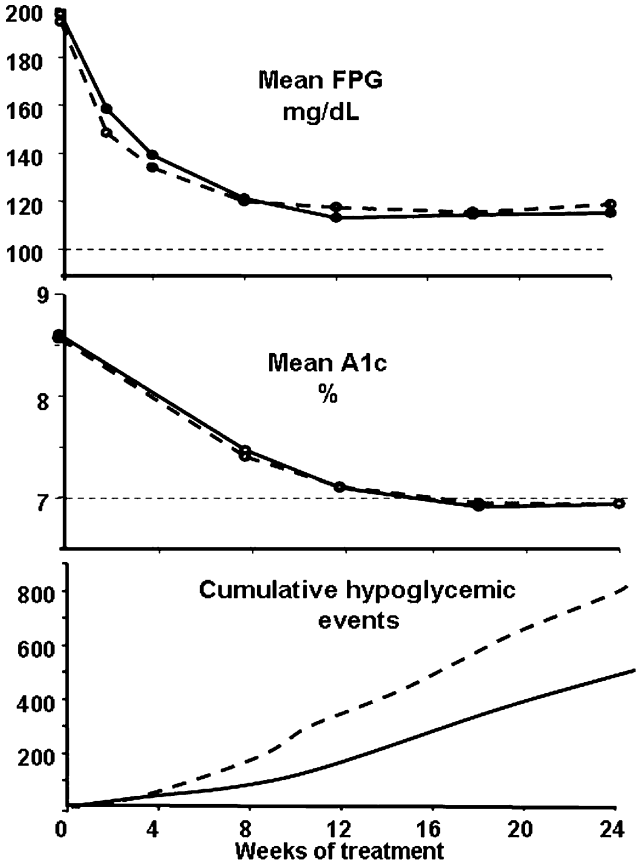


**Fig. 1.** Twenty-four week results of systematic titration of a single injection of NPH or glargine as basal insulin, added to oral antihyperglycemic agents, in the Treat-to-Target Trial *(37)*. (**A**) Mean fasting plasma glucose; (**B**) Mean hemoglobin A1c; (**C**) Cumulative numbers of hypoglycemic events confirmed by plasma-referenced capillary glucose measurement ≤56 mg/dL (3.1 mmol/L). Of 756 patients randomized, 91% completed the study.

8.9 to 7.5%. By randomizing the patients into 4 treatment-groups, the investigators demonstrated that this result was unaffected by whether point-of-care A1c measurements were available, and very little affected by whether insulin dosage was adjusted intermittently by clinic personnel or more frequently by the participants themselves. Self-titration by participants obtained a 0.2% greater reduction of A1c, and slightly reduced the frequency of hypoglycemia. The findings suggest this method can be used in clinical practice as well as in research settings, and that management of insulin doses by patients does not lead to greater risks.

Insulin detemir is another longer acting insulin analogue, which has recently been released for clinical use. Like glargine, detemir has a less pronounced peak of action and less day-to-day variability than human insulins, leading to less risk of hypoglycemia. However, it appears to have a more prominent peak and shorter duration of action than glargine *(40)*, and many patients are likely to require twice daily injections for optimal results. Although most published studies have evaluated patients with type 1 diabetes, it may be effective as a basal insulin supplement for patients with type 2 diabetes. A recent trial tested the use of either NPH or detemir, taken twice daily, with continuation of prior oral therapies *(41)*. Insulin dosage was systematically titrated as in the Treat-to-Target trial, comparing once daily detemir or NPH, with equally good glycemic control with detemir or NPH (A1c 6.8 and 6.6%), and 47% less hypoglycemia with detemir.

### *Prandial Insulin*

Alternatively, insulin can be started with an injection of human regular insulin *(42)* or one of the rapid-acting insulin analogues (aspart, lispro, or glulisine) before each meal *(43–45)*. In general, oral therapies are continued when prandial insulin is started.

In perhaps the most informative of the published studies, 80 patients taking only a sulfonylurea were randomized to add either human NPH insulin at bedtime or an injection of human Regular insulin before each meal for 4 mo *(42)*. The participants' mean duration of diabetes was 9 yr, mean BMI was 26, and mean A1c at baseline was 9.1%. The dosage of NPH was titrated seeking FPG 120 mg/dL, and the dosage of each injection of Regular insulin was adjusted with the aim of keeping glucose levels 2 h after meals less than 160 mg/dL. After 4 mo of treatment, A1c was reduced to 7.5% with 1 injection of NPH and 7.1% with 3 injections of Regular insulin. The group treated with prandial insulin gained more weight (3.4 versus 1.9 kg) than the group taking NPH.

Approval of the first inhalable insulin preparation (Exubera™) adds another option for prandial insulin delivery. This preparation has an onset of action that is as rapid as insulin lispro and a duration of effect that longer than lispro's and similar to that of regular human insulin *(46)*. Thus, it might be used as a substitute for either of these injectable insulins. A large clinical trial has examined the effects of Exubera™ in 309 patients with type 2 diabetes *(47)*. Their mean duration of diabetes was about 9.5 yr and mean BMI was 30. About 90% of them were taking metformin and a sulfonylurea. The participants were randomized to treatment for 3 mo with 1 of 3 regimens: continued oral therapy alone, inhaled insulin alone, or continued oral therapy with inhaled insulin before each meal. Mean baseline A1c was 9.5% and continued oral therapy alone reduced A1c only to 9.0%. With inhaled insulin alone A1c declined to 7.9%, and with inhaled insulin combined with prior oral therapies A1c declined to 7.3%. The mean, placebo-adjusted weight-gain for the combined therapy group was 2.7 kg.

### *Premixed Insulin*

Premixed combinations of rapid or short-acting with intermediate-acting insulins are widely used in clinical practice. Typically they are given twice daily, before breakfast and before the evening meal. Studies show that the usual 70/30 or 75/25 mixtures (70 or 75% intermediate-acting with 25 or 30% rapid or short-acting) produce a single peak of insulin action intermediate between the peaks of the individual components *(48,49)*, and 2 injections therefore provide 2 large peaks daily.

Two studies have directly compared human premixed insulin with an insulin analogue mixture *(50,51)*. The A1c values achieved were very similar in both studies and with both human and analogue insulin mixtures.

Figure 2 shows the glycemic profiles from both studies, illustrating several important points. First, the profiles from the two studies are remarkably similar, despite testing different products with somewhat different study-designs. Second, a reduction of glycemic increments after breakfast and dinner was obtained with both analogue mixtures compared to the human insulin mixtures. Whether this difference is clinically important is not clear, especially considering the equivalent A1c values. Third, a probable cause for the disappointingly high A1c values is evident in each study. A prominent decline of glucose occurred before lunch with all the insulin mixtures, suggesting a serious mismatch between physiologic requirements and the insulin concentrations in plasma at that time. This strong tendency toward hypoglycemia in the late morning must, for many patients, prevent a further increase of insulin dosage and limit further improvement of A1c.

Two other trials have further clarified the clinical effects of treatment with twice daily premixed insulins with systematic titration of dosage and comparison with systematically titrated glargine. Their results are shown in Table 1 in comparison with those of the Treat-to-Target Trial. The first of these (the LAPTOP study), included 371 patients previously taking metformin and a sulfonylurea who were treated for 6 mo with either human 70/30 insulin twice daily alone, or a single injection of glargine with continuation of prior oral therapy *(52)*. Starting from a mean A1c o*f* 8.8% at baseline, the premixed insulin regimen improved control to A1c 7.49%, whereas the combined glargine plus oral regimen achieved A1c 7.15%. As in the studies described above, glucose profiles measured by the patients showed that the lowest glucose value of the day tended to be in late morning with the premixed regimen, versus before breakfast with the glargine plus oral agent regimen. Despite slightly higher A1c levels, the premixed regimen without oral agents caused about twice as much hypoglycemia as the basal insulin regimen with continuation of oral agents.

The other trial (the INITIATE study) enrolled 233 patients previously treated with metformin alone or with other oral agents, and compared adding twice-daily premixed aspart 70/30 versus once-daily glargine *(53)*. Before either insulin was started, any oral agent other then metformin was stopped for a month, and mean A1c at that time was 9.7–9.8%. Both insulins were systematically titrated as in the other study. In this case, with continuation of metformin, the premixed insulin regimen achieved slightly better mean A1c than the glargine plus metformin

Table 1

Hemoglobin A1c (A1c), fasting plasma glucose (FPG), hypoglycemia rates, and weight-gain observed in four studies comparing initial insulin regimens for type 2 diabetes. Significance of differences among treatments in each study are shown by p-values in parentheses. Values shown for hypoglycemia are for events confirmed 56 mg/dL or less in the Treat-to-Target Trial *(37)* and the INITIATE study *(53)*, and for events confirmed 60 mg/dL or less in the LAPTOP study *(52)*. Specific rates of hypoglycemia are not available for the Detemir Treat-to-Target study *(41)*

| | *Glargine Treat-to-target (37)* | | *LAPTOP (52)* | | *INITIATE (53)* | | *Detemir Treat-to-Target (41)* | |
|---|---|---|---|---|---|---|---|---|
| *Treatments* | *Glar QD OAD* | *NPH QD OAD* | *Glar QD OAD* | *70/30 BID* | *Glar QD OAD* | *Asp70/30 BID OAD* | *Det BID OAD* | *NPH BID OAD* |
| A1c% | 7.0 | 7.0 | 7.2 (<0.0003) | 7.5 | 7.4 (<0.01) | 6.9 | 6.8 | 6.6 |
| FPG mg/dL | 117 | 120 | 115 (<0.0001) | 133 | 117 | 127 | 124 | 119 |
| Hypoglycemia events/patient-yr | 3.0 (<0.003) | 5.1 | 4.1 (<0.0001) | 9.9 | 0.7 (<0.05) | 3.4 | - | - |
| Weight-gain Kg | 3.0 | 2.8 | 1.4 (<0.08) | 2.1 | 3.5 (<0.01) | 5.4 | 1.2 (<0.001) | 2.8 |

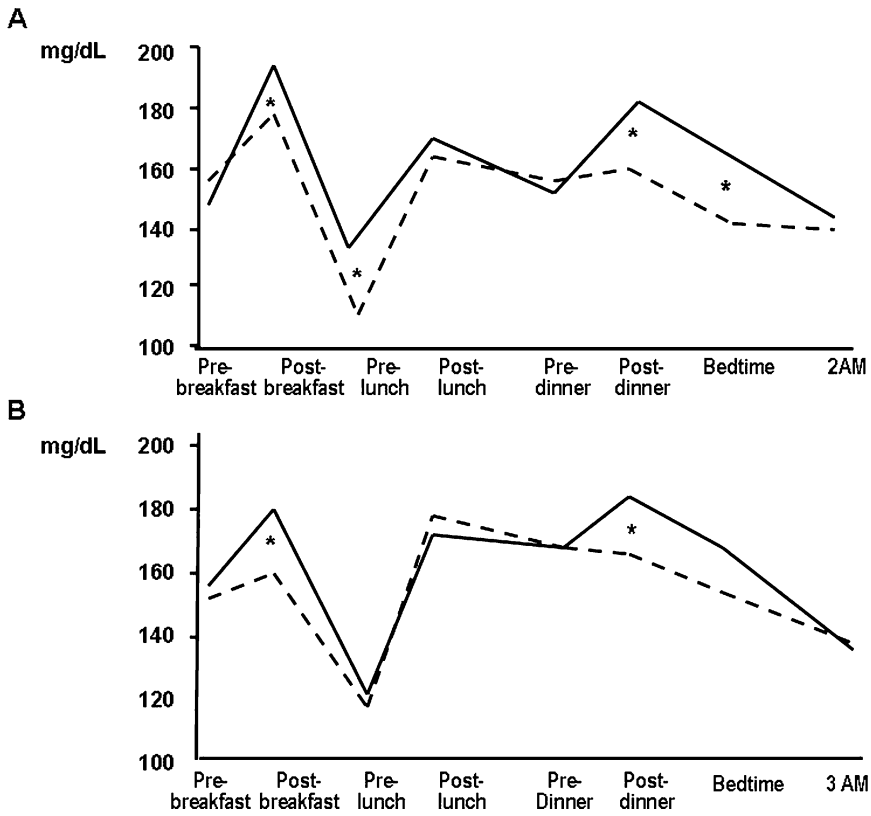


**Fig. 2.** Similarly plotted results of self-measured glycemic profiles from 2 studies comparing 3 mo of treatment with twice-daily human premixed insulin (solid lines) versus 3 mo with twice-daily analogue premixed insulin (dashed lines) unaccompanied by oral antihyperglycemic agents. In **A** (above) human 70/30 (70% NPH, 30% Regular) insulin was compared with aspart 70/30 (70% protamine-aspart, 30% unmodified aspart) in 187 patients with type 2 diabetes and 104 with type 1 diabetes *(50)* In **B** (below) human 70/30 insulin was compared with lispro 75/25 (75% protamine-lispro, 25% unmodified lispro) in 89 patients with type 2 diabetes *(51)*. The asterisks indicate between treatment-comparisons showing significant differences at specific times of day ($p < 0.05$).

regimen, 6.9 versus 7.4%. However, mean weight-gain was greater with premixed insulin (5.4 versus 3.5 kg), and hypoglycemia confirmed less than 56 mg/dL was almost 5 times more frequent with premixed insulin (3.4 versus 0.7 events per patient-year).

LAPTOP and INITIATE provide useful insights. In LAPTOP, twice-daily premixed insulin used without oral antihyperglycemic agents had less desirable results than basal insulin with oral therapy continued. This finding is consistent with previous evidence that combinations of agents are usually more effective than monotherapy, and suggest that (at least in type 2 diabetes) switching directly from any oral regimen to insulin alone is not likely to be a wise choice. In INITIATE, twice-daily premixed insulin, assisted by continuation of oral therapy and aggressively titrated, achieved better A1c levels than basal insulin with oral therapy, but accompanied by more hypoglycemia and weight-gain.

## TRANSITION TO BASAL-BOLUS INSULIN

With all 3 of the methods of initiating insulin therapy described above, many patients do not reach the 7% A1c target, and many of those who do subsequently experience gradual worsening of control over time. How treatment can be further intensified is therefore an important consideration in comparing ways to start insulin. In the case of regimens using only basal insulin or only prandial insulin, the next step is clear. When basal insulin alone is insufficient, add prandial insulin; when prandial insulin alone is insufficient, add basal insulin. In the case of the twice-daily premixed regimen, the next step is not obvious either from theoretical considerations or from experimental evidence. A recent study addresses this dilemma *(54)*. Sixteen patients previously taking

twice-daily 70/30 human insulin were assigned, in random sequence, to each of two 3-injection regimens each using only analogue premixed insulins for 4 wk. Both a regimen consisting of aspart 70/30 insulin with each meal, and one consisting of aspart 70/30 with breakfast and lunch but aspart 50/50 with dinner improved daytime glucose patterns, but neither of these improved postdinner or overnight glycemic control. This study highlights the difficulty of converting patients who are not well controlled with twice-daily premixed insulin to a more physiologically appropriate insulin regimen. In clinical practice, twice-daily premixed insulin therapy may come to a dead-end, with no further alteration of therapy despite inadequate glycemic control. Devising and testing ways to ease the transition from an initial insulin regimen to full basal-bolus therapy is an important issue, but beyond the scope of this chapter.

## TREATMENT RECOMMENDATIONS

The studies reviewed above provide guidance on how to progress from oral therapies alone to regimens including insulin. As mentioned at the beginning of this chapter, 3 antihyperglycemic agents enjoy by far the most extensive experience defining their adverse effects, demonstrating tactics for their use, and proving their medical benefits. These are: metformin, sulfonylureas, and insulins. In addition, formulations of these agents have improved greatly over time, and they are relatively inexpensive. The scheme proposed here is therefore based on these agents *(1)* (Table 2).

### *Oral Monotherapy and 2-Agent Combination Therapy*

Currently available evidence supports beginning antihyperglycemic drug therapy with either metformin or a sulfonylurea (other than glyburide). When oral monotherapy is no longer sufficient, addition of the other oral agent usually restores glycemic control. After 5–10 yr treatment is likely to require further intensification.

### *Addition of Basal Insulin*

Adding a single injection of longer-acting insulin to supplement endogenous basal insulin secretion is the next step. Several features support this choice. The adverse effects are well known and acceptable, and only 1 daily injection and 1 daily glucose test are needed. Self-adjustment of dosage based on fasting glucose values, by the patient, is logical and easy to learn. Initial dosage may be arbitrary (10 units at bedtime is a common choice), or based on body weight (for example, 0.1 or 0.15 units per kg). Either human NPH insulin or glargine may be used. Both can be effective, but glargine causes less hypoglycemia. Experience with detemir is limited, but it

**Table 2**
**Levels of evidence supporting treatment recommendations References and explanations supporting this classification are provided in the text**

| | *Glycemic control* | *Microvascular benefits* | *Cardiovascular benefits* | *Ovarall rating* |
|---|---|---|---|---|
| Standard treatments alone or in combination | | | | |
| Metformin | 1A | 1A | 1B | 1A |
| Sulfonylureas | 1A | 1A | 2A | 1A |
| Basal insulin | 1A | 1A | 2A | 1A |
| Prandial or premixed insulin alone or with basal insulin, sulfonylurea, or metformin | 1A | 1C+ | 1C+ | 1B |
| Newer agents for individualized use | | | | |
| Alphaglucosidase inhib | 1A | 1C+ | 1B | 1B |
| Rapid secretagogues | 1A | 1C+ | 1C+ | 1B |
| Thiazolidinediones | 1A | 2A | 2B | 1C+ |
| Exenatide | 1A | 2C | 2C | 1C |

Table 3
Methods for adjusting the dosage of basal insulin used in the Treat-to-Target Trial *(37)* and the LANMET Study *(38)*

| | *Treat-to-Target Trial (37)* | *LANMET STUDY (38)* |
|---|---|---|
| Starting dose | 10 units | 10 or 20 units |
| Frequency of titration | Weekly | 2–3 times weekly |
| Insulin increments | | |
| Glucose range mg/dL | | |
| >180 | 8 units | 4 units |
| 140–180 | 6 | 2 |
| 120–140 | 4 | 2 |
| 100–120 | 2 | 2 |

also seems effective for basal insulin supplementation when taken twice-daily. Whatever insulin is used, the best results occur when at least 1 oral therapy is continued.

### *Titration of Basal Insulin to Optimal Dosage*

The underlying principles of titration are more important than the details of the method used. The key issues are: identifying a target glucose value, measuring fasting glucose regularly, increasing the dosage of insulin according to a predefined plan, and doing so at regular intervals until the target is reached or hypoglycemia prevents further increase. Two successful methods, those used in the Treat-to-Target Trial and in the LANMET study, are described in Table 3.

Two aspects of titration remain less well defined, and require clinical judgement. One issue concerns the fasting glucose level chosen as the target. A value that is too high (probably any value above 120 mg/dL) will lead to premature cessation of titration for many patients. A value too low (probably any value below 90 mg/dL for patients with diabetes for more than 5 yr) may lead to an unacceptable rate of hypoglycemia. In general, studies have settled on target levels between 100 and 110 mg/dL for typical patients. A related question is what warning signals demand that titration cease before the target is reached. A hypoglycemic event requiring assistance by another person is an obvious warning to reduce insulin dosage. Also, repeated events that are less serious but documented by glucose measurements below 70 mg/dL generally call for cessation of titration. For some patients, highly variable glucose values accompanied by marked variations of daily schedule and meal-patterns may require stopping titration.

The mean insulin dosages used in the Treat-to-Target and LANMET studies are of interest because they reflect typical requirements for success under different conditions. In the Treat-to-Target Trial most patients were taking 2 oral agents, and the mean daily insulin dose was about 0.45 units/kg of body-weight. In the LANMET study all patients were taking 1 oral agent (metformin), and the mean insulin dose was close to 0.7 units/kg of body-weight. The greater mean dosage in LANMET may have resulted in part from more sustained and aggressive titration, but the lack of a second oral agent must have contributed as well. In clinical practice the titration of insulin often ceases at much lower doses, leading to less improvement of glycemic control than would be possible. For this reason, patients must be taught the principles of insulin adjustment and eventually become responsible for most titration decisions.

### *Transition from Basal Insulin to More Complex Insulin Regimens*

If A1c 7% is not achieved with basal insulin added to oral therapy, after a trial of 6 mo of titration of insulin, prandial insulin can be added. Patients who do not have A1c at target using a basal insulin regimen usually have fasting glucose higher than 100 mg/dL, and before-dinner glucose values higher than 140 mg/dL. Of the times glucose testing is commonly done, the bedtime value is likely to be the highest of the day. In addition, the first meal of the day is usually followed by a sizable increment of glucose. On the basis of these observations, adding an injection of Regular insulin or a rapid-acting insulin analogue before either the first meal or the evening meal would likely improve the glucose pattern significantly. Because individuals have widely differing meal patterns,

beginning intensification of a basal insulin regimen by adding an injection prior each person's main meal of the day is a logical tactic. Stepwise addition of prandial injections before other meals might follow. Much remains to be learned about the best ways to proceed from basal to basal-bolus therapy, but this process seems more promising than intensification of premixed insulin regimens.

### *Use of Individualized Alternative Regimens*

As suggested earlier, some patients may, for various reasons, be treated very effectively with other methods. Patients with extreme aversion to insulin injections and only moderately elevated A1c may use a TZD as the third agent, rather than insulin. For a patient with severe weight-related problems, such as, for example, peripheral edema leading to breakdown of skin of the lower legs, the tendency of both TZDs and insulin to cause further gain of weight may make exenatide a preferable alternative. When fasting glucose is nearly normal but postprandial hyperglycemia is very prominent, as can occur during glucocorticoid treatment or after alcoholic (or other forms of) pancreatitis, beginning insulin treatment with prandial insulin alone is very appropriate. Use of inhaled formulations may improve the acceptability of prandial insulin for some patients, although this possibility needs further confirmation in the setting of clinical practice. When renal insufficiency or multisystem illness precludes use of oral therapies, and limits the value and increases the risks of seeking 7% A1c, twice daily premixed insulin adjusted to conservative glycemic targets may be the best choice. Finally, a potential alternative to basal-bolus treatment for patients with good control of fasting glucose but excessive daytime hyperglycemia during treatment with basal insulin and oral agents is adding an injected agent with the ability to limit postprandial hyperglycemia. Exenatide should be effective in combination with basal insulin, and pramlintide, an analogue of the hormone amylin, might be injected before meals with similar effects. Both of these options deserve objective testing to define their risks and benefits.

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# 12 Intensive Insulin Therapy in T2DM

*Steven V. Edelman*

***CONTENTS***



## INTRODUCTION

Intensive insulin therapy requires multiple daily injections of basal-bolus strategies to achieve glucose control. Intensive insulin therapy is commonly employed in patients unable to achieve adequate glucose control with combination oral therapies; however, it can be used at any stage of Type 2 diabetes milletus (T2DM). Owing to the natural history of T2DM, characterized by progressive loss of beta cell function over time, insulin regimens may need to be intensified over time. For example, an individual with T2DM failing oral agents but with some beta cell function may do very well on a basal insulin and only 1 prandial dose of a fast acting analog. This situation is dramatically different from type 1 diabetes where a prandial dose is needed before all meals and most snacks.

Successful insulin management ideally requires an educated and motivated patient, as well as the participation of a multidisciplinary health care team. Intensive insulin therapy initially requires substantial input by the caregiver and support staff, which may have an economic impact on the health care system *(1)*; however, over time, an educated patient will require fewer staff resources. Although long-term data on costs are not yet available, projections suggest that substantial savings from the high costs of end stage disease could be achieved if intensive insulin therapy achieves levels of glucose control consistent with ADA guidelines *(2)*.

## HETEROGENEITY OF T2DM

The variable time course of beta cell dysfunction in T2DM and the heterogeneity in the pathophysiology of T2DM may influence when patients require insulin. Some patients diagnosed with T2DM may actually have latent autoimmune diabetes in adults (LADA), characterized by severe insulinopenia, islet cell antibody (ICA) positivity or antibodies to glutamic acid decarboxylase (GAD), decreased C-peptide response to glucagon stimulation, and

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a propensity for primary and secondary oral medication failure *(3,4)*. These individuals typically require early transition to insulin therapy. Wide geographic and racial differences also influence the need for insulin therapy. For example, Asian patients with T2DM tend to be thinner, are diagnosed with diabetes at an earlier age, fail oral hypoglycemic agents sooner, and are more sensitive to insulin therapy than the classic centrally obese patient in the United States and some parts of Europe *(5)*.

## SPLIT MIXED INSULIN REGIMENS

One of the most common insulin regimens used in T2DM is the split-mixed regimen, consisting of a prebreakfast and predinner dose of a mixture of intermediate- and fast-acting insulin. In a landmark trial by Henry et al *(6)*, daylong glycemia and glycosylated hemoglobin (HbA1c) were essentially normalized by 6 mo of intensive therapy with a split-mixed insulin regimen.

The average total insulin dose needed to maintain glycemic control approached 100 units per day (~1 unit per kg body weight), with approximately 50% of the total dose required before breakfast and 50% before dinner. The ratio of NPH to regular insulin was approximately 75%:25% (Table 1). There was a very low incidence of mild hypoglycemic reactions, which decreased as the study progressed, and no reactions were severe or required assistance. The exacerbation of hyperinsulinemia by exogenous insulin therapy was strongly correlated with weight gain throughout the study as was the total insulin dose. Despite biweekly visits with the study dietitian and instructions to reduce the daily caloric intake, a mean weight gain of approximately 9 kg (18.8 pounds) occurred.

This study emphasizes a number of important aspects of intensive glucose control with insulin in obese subjects with T2DM. First, the average daily dose of insulin needed to control such patients approx 1 unit per kilogram of body weight. Second, the total daily insulin requirement can be split equally between the prebreakfast and predinner injections, unlike the usual two thirds/one third recommendations. Third, the split-mixed regimen in patients with T2DM is usually devoid of early morning hypoglycemia and fasting (preprandial) hyperglycemia, commonly seen with type 1 diabetes. Fourth, both severe and mild hypoglycemic events are much less frequent in patients with T2DM compared to those with type 1 diabetes undergoing intensive insulin therapy. Finally, weight gain correlates with peripheral hyperinsulinemia and the total amount of insulin used.

Another long-term (5-yr) clinical trial using a split-mixed regimen of 2 injections per day in 102 nonobese type 2 diabetic patients demonstrated that excellent glycemic control could be achieved with intensive split-dose

**Table 1**
**Insulin requirements, caloric intake by patient recall and body weight during 6 months of intensive insulin therapy. Note the 8.7 Kg weight gain despide the reduced caloric intake**

| | *Months of insulin treatment* | | | |
|---|---|---|---|---|
| *Parameter* | *0* | *1* | *3* | *6* |
| Total insulin dose (U) | – | 86 ± 13 | 92 ± 16 | 100 ± 24 |
| NPH | – | 65 ± 10 | 69 ± 12 | 74 ± 16 |
| Regular | – | 20 ± 4 | 23 ± 5 | 26 ± 9 |
| Insulin distribution (U) | | | | |
| AM Dose | – | 41 ± 9 | 47 ± 9 | 51 ± 13 |
| % NPH% Regular | | 76/24 | 77/23 | 76/24 |
| PM Dose | – | 45 ± 6 | 45 ± 7 | 49 ± 12 |
| % NPH% Regular | | 76/24 | 73/27 | 72/28 |
| Body weight (Kg) | 93.5 ± 5.8 | 97.2 ± 5.9 | 100.5 ± 67.5* | 102.2 ± 6.8* |
| Weight gain (Kg) | | 3.7 ± 1.0 | 7.0 ± 1.5 | 8.7 ± 1.9 |
| Caloric intake† (Kcal/day) | 2023 ± 138 | 1937 ± 122 | 1918 ± 121 | 1711 ± 119 |

Values are means ± SE.
*P < 0.05 by Scheffe's F test.
†Estimated by 24-h recall.

insulin without significant hypoglycemia but at the expense of progressive weight gain *(7)*. All these studies clearly demonstrate the efficacy of various insulin regimens and the adverse consequences of such therapy.

## PREMIXED INSULIN REGIMENS

Combinations of rapid-acting insulin analogs and intermediate acting insulins are manufactured as premixed insulin formulations. Premixed regimens are not appropriate for patients with type 1 diabetes and for most thin, insulin sensitive patients with T2DM; however, they can be effective for obese insulin resistant patients with T2DM. One such insulin preparation is Humalog Mix 75/25, which is a fixed-ratio mixture of 25% rapid-acting insulin lispro and 75% novel protamine-based intermediate-acting insulin called neutral protamine lispro (NPL). NPL was developed to solve the problem of instability with prolonged storage that occurs with NPH combined with short acting insulin. Studies of the pharmacokinetic and pharmacodynamic profiles of NPL show they are comparable to those of NPH insulin *(8)*.

Humalog Mix 75/25 was compared to premixed human insulin 70/30 in patients with T2DM in a 6-mo randomized, open-label, 2-period crossover study *(9)*. Twice-daily injections of Humalog Mix 75/25 resulted in improved postprandial glycemic control after the morning and evening meals, reduced rate of nocturnal hypoglycemia, similar overall glycemic control, and the added convenience of administration immediately before meals. Humalog Mix 50/50 is also now available for those patients whose post prandial glucose values are not adequate on the 75/25 and 70/30 combinations.

Insulin aspart, another rapid-acting insulin analog, is available in a premixed formulation with a protamine-retarded insulin aspart called Novolog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart). A comparison study *(10)* of the pharmacokinetic and pharmacodynamic parameters of the Novolog Mix 70/30 and human insulin 70/30 in healthy patients showed that the faster onset and greater peak action of insulin aspart was preserved in the aspart mixture.

Another study *(11)* compared premixed aspart mixture 70/30 with premixed human insulin 70/30 administered twice daily in a randomized 12-wk open-label trial in 294 patients with type 1 or T2DM. Treatment with twice-daily premixed aspart mixture 70/30 resulted in similar overall glycemic control; yet postprandial control improved without additional hypoglycemia and with injections immediately before meals compared with premixed human insulin 70/30 given 30 min before the meal.

## PREMIXED INSULIN TWICE DAILY INJECTIONS VERSUS BASAL INSULIN ALONE

Premixed insulins have been compared to regimens consisting of basal insulins alone in several clinical trials *(12–16)*. The titration scheme that may have relevance to clinical practice used in the study is shown in (Table 2). To begin therapy, 12 U Novolog Mix 70/30 were given to insulin-naïve patients. For insulin-users, those on < 30 U

**Table 2**
**Titration algorithm for Novolog Mix 70/30 used up to 3 times a day *(17)***

| *Blood glucose measure Predinner (for OD and BID Novolog Mix 70/30) Prebreakfast (for BID Novolog Mix 70/30)* | | | *Blood glucose measure Prelunch (for TID Novolog Mix 70/30)** | | |
|---|---|---|---|---|---|
| *mg/dL* | *mmol/L* | *Insulin dose adjustment (U)* | *mg/dL* | *mmol/L* | *Insulin dose adjustment (U)* |
| <80 | <4.4 | −3 | n/a | n/a | n/a |
| 80–110 | 4.4–6.1 | 0 | <100 | 4.4–6.1 | –3 |
| 111–140 | 6.2–7.8 | +3 | 100–140 | 6.2–7.8 | 0 |
| 141–180 | 7.83–10 | +6 | 141–180 | 7.83–10 | +3 |
| >180 | >10 | +9 | >180 | >10 | +6 |

*People using Novolog Mix 70/30 TID could also adjust breakfast and dinner doses, but it was not recommended that more than 1 dose be adjusted at a time.

were transferred to the identical unit dose of Novolog Mix 70/30; for those on 31–60 U, the Novolog Mix 70/30 dose was started at 70% of the previous insulin dose. The dose was titrated based on average plasma glucose values from 3 previous days. In two separate studies, both Novolog Mix70/30 or Humalog Mix 75/25 given twice daily in conjunction with metformin, allowed more patients to reach target glucose control, than glargine of basal insulin administered once-daily with metformin *(12,13)*.

More recently, a treat-to-target trial in 100 patients poorly controlled with oral agents with or without insulin utilized the stepwise addition of premixed insulin until glycemic targets were attained *(14)*. Using only 1 injection of Novolog Mix 70/30 daily, a total of 41% of patients were able to reach the ADA target of HbA1c $<7.0\%$ and 21% reached the AACE/IDF target of $\leq 6.5\%$. This increased to 70% and 52% of subjects when twice-daily injections were used (among those not achieving $HbA_{1c} \leq 6.5\%$ with once-daily therapy), and 77% and 60% when the small number of patients requiring 3 times daily administration was accounted for. This was accomplished without increasing the frequency of major or minor hypoglycemic episodes over that reported for once- or twice-daily use.

In a different 24-wk study, 364 insulin-naïve patients with a baseline A1c of 8.84% on both a sulfonylurea and metformin were either continued on oral agents, and given glargine once daily, or given human premixed insulin twice daily (before breakfast and dinner) with discontinuation of oral agents *(15)*. After 6 mo, the glargine plus oral agents group had a significantly greater reduction in A1c ($-1.64\%$) compared to the human premixed insulin alone without oral agents twice daily group ($-1.30\%$), $p < 0.0005$. In addition the glargine group used less insulin, had fewer documented hypoglycemic reactions and less weight gain.

As demonstrated in three studies, the comparison of basal insulin vs. premixed can result in very different outcomes and conclusions depending on protocol design. When oral agents are continued, glargine at bedtime did better in terms of glycemic control than premix twice a day without oral agents. The ultimate results of these comparison studies depend on the patient characteristics, use of analog mixtures, continuation of oral agents, and number of injections per day.

## BASAL BOLUS INSULIN REGIMENS

Basal–bolus insulin strategies, which can be used in patients with either T1DM or T2DM incorporates the concept of providing continuous basal insulin levels in addition to brief increases in insulin at the time of meals via bolus doses *(16)*.

The goals of therapy should be tailored to each patient individually. Candidates for intensive management should be motivated, compliant, educable, and be without other medical conditions or physical limitations that preclude accurate and reliable home glucose monitoring (HGM), continuous glucose monitoring (CGM), or insulin administration. Caution is advised in elderly patients or those with hypoglycemic unawareness in whom the goals of therapy may need to be relaxed. High titers of insulin antibodies, especially in patients with a history of intermittent use of impure insulins of animal origin may also impede insulin therapy.

It has been estimated that 50% of the day to day variation in glucose values is owing to intra-subject variation in absorption and time course of action. Consistency is important to reduce fluctuations in glucose values. The site of injection may alter insulin pharmacokinetics and absorption, especially if lipohypertrophy is present. The periumbilical area is the preferred site to inject insulin because of the rapid and consistent absorption kinetics observed at this location; however, rotating the injection site is usually advised. It is also advisable to inject in the same body location for a certain meal time (i.e., triceps fat pad for breakfast, abdomen for lunch, and upper thighs for dinner).

### *Selecting Patients for Intensive Insulin Therapy*

Insulin-naive patients with T2DM who are unable to achieve or maintain glycemic goals on oral agents can advance therapy to basal insulin plus oral agents and then advance to basal-prandial therapy in a stepwise manner. Prandial insulin is added to the regimens of patients not achieving glycemic goals despite well-controlled FBG after 3 mo of basal insulin *(19)*. Initially, prandial insulin therapy may only need to be provided with the largest meal of the day, or whichever meal produces the greatest postprandial glucose excursions from baseline.

Certain patients with newly diagnosed T2DM may benefit from early initiation of basal-prandial insulin therapy, including those with glucose toxicity or LADA. LADA is caused by immune-mediated destruction of the insulin-producing pancreatic β-cells, similar to type 1 diabetes, but typically is diagnosed in patients aged 30–60 yr (the diagnosis is confirmed by blood tests for the presence of glutamic acid decarboxylase antibodies). Patients with LADA generally do not respond adequately to oral agents, and will require insulin therapy at an earlier stage than other patients with T2DM *(17,18)*.

Newly diagnosed patients with A1C >10.0% require more than a 3.0% reduction in A1C to achieve target glucose levels recommended by the ADA *(19)*. Because reductions in A1C of this magnitude generally will not be achieved with oral agents alone, especially in the face of glucose toxicity, such patients who are symptomatic should be started on insulin immediately. Once insulin has successfully reversed glucose toxicity, many of these newly diagnosed patients can then be controlled on oral agents alone *(20)*.

## BASIC CONCEPTS OF BASAL BOLUS STRATEGIES

An individualized regimen may incorporate insulins of varying onset of action, peak, and duration (Table 3). The use of premeal regular insulin with bedtime NPH as the basal insulin has been a common strategy for intensive insulin therapy in the United States over the past decade. Because regular insulin should be administered 30 to 45 min before meals, a short term risk of hypoglycemia exists if the meal is delayed, and there is a risk of delayed hypoglycemia because of the overlap of pharmacodynamics of regular and NPH insulin. As a result, use of regular insulin may be complicated by high postprandial glucose levels and delayed hypoglycemia. An alternative strategy is the mealtime administration of rapid acting insulin analogs in combination with long-acting basal insulin, such as glargine or detemir *(21–23)*. Regimens that use multiple doses of intermediate acting insulin such as NPH (usually only 2) can be associated with unpredictable nocturnal hypoglycemia and day-to-day instability of blood glucose patterns, in part because of intra-patient variability in the peak action profile of NPH. NPH, which is commonly given twice daily exhibits its peak action ~4 to 8 h after administration, has also been used in combination with rapid-acting insulin analogs, Because of its time to peak action, NPH should ideally be given every 6 h or 4 times per day to be effective as a true basal insulin. NPH given 4 times a day would be difficult to implement and is not needed with the availability of long-acting insulin analogs.

Improved mealtime glucose control with the rapid-acting analogs has exposed the gaps in basal insulin coverage provided by therapy with the traditional intermediate insulin preparations. Taking a long-acting basal insulin analog (e.g., glargine or detemir) with a relatively constant and flat pharmacokinetic profile once or twice a day will result in a more physiologic pattern of basal insulin replacement. Insulin glargine has been available in the United States since 2000 and in combination with a rapid-acting insulin analog has demonstrated effective glycemic control and a lower incidence of nocturnal hypoglycemia than other insulin preparations currently used for basal insulin supplementation *(28,30,31)*.

In a 22-wk randomized trial, 395 people with T2DM were randomized to a regimen using insulin aspart + insulin detemir, the newest basal insulin to become available, versus regular human insulin + NPH *(24)*. Basal insulins were given once or twice daily, in accordance with prior treatment, and oral agents were discontinued. Treatment

**Table 3**
**Comparison of human and analogue insulins***

| *Insulin preparations* | *Onset of action* | *Peak* | *Duration of action* |
|---|---|---|---|
| Lispro Aspart Glulisine | 5−15 minutes | 45−90 mins | 3−5 hours |
| Human Regular | 30−60 minutes | 2−4 hours | 6−8 hours |
| Human NPH | 2−3 hours | 6−8 hours | 10−18 hours |
| Detemir | 1−2 hours | ~12−16 hours; relatively flat | Up to 24 hours |
| Glargine | 1−2 hours | Peakless | ~24 hours |

Ref (7)

*The time course of action of any insulin may vary in different individuals depending on the degree of obesity, site of injection and ambient glucose level at the time of injection.

with insulin detemir + aspart produced equivalent glycemic control to a similar regimen using NPH + regular insulin (HbA1c 7.46 versus 7.52%, respectively), but with less weight gain (0.52 versus 1.13 kg, $p = 0.038$) and less within-person variability in HGM (SD 21.6 versus 27.7 mg/dL, $p < 0.001$). Safety profiles were similar between the 2 treatments.

## PRACTICAL RECOMMENDATIONS FOR INITIATION OF BASAL PRANDIAL INSULIN

Initiation of basal insulin is normally an important first clinical maneuver in patients failing oral agents. Some patients with T2DM may have enough endogenous basal insulin secretion to allow for improved glycemic control with prandial insulin alone. This phenomenon was seen with an inhaled insulin study that will be discussed below. Nonetheless, initiation of basal insulin is normally key to a successful intensive insulin regimen *(25)*. The options for initiating basal insulin include: 1) insulin glargine given once daily, 2) insulin detemir once or twice daily, or 3) NPH given 2–4 times daily depending on HGM results. Patients should not experience hyper or hypoglycemia while fasting if the basal insulin dose is adjusted properly. A typical starting dose is 10 units of basal insulin, however most obese patients with T2DM will need approximately 40–60 units per day. Frequent follow-up to review HGM data is required to make the proper adjustments.

If A1C goals are not achieved after a period of 3–6 mo of treatment with basal insulin plus oral agents, patients should be instructed to monitor glucose preprandially and/or 1–2 h after each meal on a rotating basis to identify the main meal that is contributing to hyperglycemia. Once identified, 5–10 U or 0.1 units/100Kg body weight of rapid-acting insulin should be administered before this meal. Adjustment of the dose is made on HGM results within 1 to 2 h after the meal or simply the blood glucose results before the next meal, or bedtime. If A1C goals are still not reached after 3–6 mo of basal insulin, oral agents, and 1 prandial insulin injection at the main meal, prandial insulin can be added before other meals based on home glucose monitoring as described above. Rapid-acting insulin doses should continue to be titrated according to home glucose monitoring data (either post prandial values or the glucose value before the subsequent meal). The amount of increase in the dose will depend on the total daily insulin dose (basal and prandial) in addition to the glucose levels. If the total daily insulin dose is less than 50 units then increase in the prandial dose should be in increments of 3 to 5 units at a time ($< 10\%$). For patients on large daily doses of insulin changes of 5 to 10 units (40%) may be more appropriate. As the patient's blood glucose levels approach goal, the changes in insulin doses should be more modest. Caution should also be taken in the elderly and in patients with hypoglycemia unawareness. Continuous glucose monitoring can help determine the correct dose safely.

## IMPLICATIONS OF BASAL-PRANDIAL REGIMENS FOR EXISTING ORAL AGENTS

As a general rule the oral agent regimen should be continued until the addition of insulin achieves glycemic control goals. As glycemic control is established (A1C $< 7.0\%$), the oral agents should be evaluated (reduced dose or discontinue) in patients on basal-prandial insulin therapy. Doses of sulfonylurea should be discontinued or reduced by $\geq 50\%$ as necessary, especially if hypoglycemia occurs. If subsequent monitoring clearly shows prompt loss of control, the original dose of oral agent should be resumed or upward titration of the insulin. For patients receiving metformin, thiazolidinediones, and/or DPP4 inhibitors, the decision to continue and/or adjust doses may be left to the discretion of the physician. Typically, if significant glycemic benefit with the oral agent was achieved before starting insulin therapy it may be beneficial to continue the drug.

## EXTERNAL INSULIN PUMP THERAPY

External insulin pump therapy or continuous subcutaneous insulin infusion (CSII) has been used traditionally in patients with type 1 diabetes. However, insulin pump therapy is extremely valuable in patients with T2DM who require insulin but who have not achieved glycemic control with subcutaneous injections or who are seeking a more flexible lifestyle *(26)*. As seen in T1DM, insulin pump therapy allows for increased flexibility in meal timing and amounts, increased flexibility in the timing and intensity of exercise, improved glucose control while reducing the daily variability of blood glucose values and incidence of hypoglycemia. Although not documented well in clinical trials, many experts believe that because of the more physiologic delivery of insulin, glucose

control is achieved with less insulin than that needed in a subcutaneous insulin regimen. This may be caused by a reduction in glucose toxicity and improvement of insulin resistance and beta-cell secretory function as a result of improved glycemic control with pump therapy. Weight gain may be lessened if the patient requires less insulin than was used before insulin pump therapy. In addition, with the reduction of hypoglycemic events, there is less overeating to compensate for excessive insulin.

Because pumps deliver constant infusions of regular or fast-acting insulin, there is no peaking or waning of activity of injected intermediate- and long-acting insulins, which do not provide as constant a basal rate owing to variable absorption and pharmacokinetics. Insulin pump therapy may allow for more reliable insulin absorption and pharmacokinetic profile, resulting in improved reproducibility in insulin availability and reduced fluctuations in glycemic control *(27)*.

Presently, there is a paucity of clinical trials using insulin pumps in T2DM, but pump therapy is a viable option in insulin-requiring patients with T2DM who are unable to achieve adequate glycemic control with multiple-injection regimens. Although some studies demonstrate metabolic benefits of pump therapy in T2DM, all are limited by a relatively short period of evaluation and a small number of heterogeneous subjects. Interpretation of these studies is further confounded by the random assignment of subjects to dissimilar conventional insulin regimens, making comparison between studies difficult.

Garvey et al *(28)* studied the effect of intensive insulin therapy on insulin secretion and insulin action before and after 3 wk of CSII therapy in 14 patients with T2DM (age 50 +/−3 yr, duration of diabetes 7.8 +/− 2.1 yr, and 119% ideal body weight). In 3 wk of therapy, the mean fasting plasma blood glucose and HbA1c values fell 46% and 38%, respectively. The mean daily insulin dose was 110 units/d, and there was a 74% increase in the insulin-stimulated glucose disposal rate, and a 45% reduction in hepatic glucose output to mean levels similar to those of normal subjects. In addition, there were significant improvements in both endogenous insulin and C-peptide secretion. This study demonstrates that pump therapy is feasible and effective at improving metabolic control and reversing glucose toxicity in these poorly controlled subjects with T2DM.

In another recent study *(29)*, 132 CSII naive type 2 diabetic patients were randomized to the pump or multiple daily injections (MDI). This study showed that pump therapy provided efficacy and safety equivalent to MDI therapy. Lower pre and post meal blood glucose values were shown by the CSII group at most time points (values were only significant 90 min after breakfast; 167 +/−47.5 mg/dL versus 192 +/− 65.0 mg/dL for CSII and MDI, respectively; $p = 0.019$).

In summary, insulin pump therapy has not been fully evaluated in patients with T2DM. From published studies, however, it is apparent that CSII therapy can safely improve glycemic control while limiting hypoglycemia. CSII may be particularly useful in treating patients with T2DM who do not respond satisfactorily to more conventional insulin treatment strategies.

## INHALED INSULIN

Insulin therapy is often delayed or suboptimally implemented in patients with T2DM. Although several factors contribute to poor implementation of insulin therapy, the inconvenience and complications, such as weight gain and poor patient acceptability, of a daily regimen of multiple injections, and psychological resistance may all play a role. These problems are being addressed by the ongoing development of alternate insulin delivery systems, including the inhaled and intranasal routes, as well as molecular modifications that may allow oral therapy.

The first alternate insulin delivery system, inhaled human insulin powder (Exubera) *(30–34)*, did become available, but was removed from the US market because of poor sales and reduced demand for the product.

## SUMMARY AND RECOMMENDATIONS

Type 2 diabetes is a common disorder often accompanied by numerous metabolic abnormalities, leading to increased rates of cardiovascular morbidity and mortality. Improved glycemia will delay or prevent the development of microvascular disease and reduce many or all of the acute and subacute complications that worsen the quality of daily life. In selected patients, intensive insulin therapy can be a successful adjunct to diet and exercise for control of hyperglycemia (Table 5). This is best achieved in a multidisciplinary setting using complementary therapeutic modalities that include a combination of diet, exercise, and pharmacologic therapy.

Table 5
Levels of evidence for insulin therapy in type 2 diabetes

| *Recommendation* | *Level of evidence* |
|---|---|
| Combination therapy (oral agents during the day in addition to a basal insulin) is an effective way to improve glucose control and minimize weight gain | 1A |
| Split mixed or premixed insulin given 2 to 3 times a day can effectively get patients with type 2 diabetes safely to goal (A1c<7%) | 1B |
| Basal bolus or mutiple daily injection regimens in type 2 diabetes is an effective way to achieve glycemic goals. | 1C+ |
| Patients with type 2 diabetes may only need 1 injection of a fast acting insulin with their largest meal in addition to a basal insulin instead of before all meals | 1C+ |
| Patients with type 2 diabetes can be treated effectively with CSII (continuous subcutaneous insulin infusion) pumps | 1C |

Emphasis should be placed on diet and exercise initially, and throughout the course of management as well, because even modest success with these therapies will enhance the glycemic response to both oral antidiabetic agents and insulin. With the development of newer insulin analogues, inhaled insulin, and pramlintide, increasing flexibility is available to tailor insulin regimens for successful use in individual patients.

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# 13 Hypoglycemia in Type 2 Diabetes

*Philip E. Cryer*

***CONTENTS***



**Summary**

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes. It can be caused by sulfonylureas or other insulin secretagogues, and perhaps by metformin, as well as by insulin. Hypoglycemia is less frequent overall in type 2 diabetes (T2DM), compared with type 1 diabetes (T1DM). However, it becomes a progressively more frequent problem, ultimately approaching that in T1DM, in advanced (i.e., insulin deficient) T2DM because of compromised glucose counterregulation – the syndromes of defective glucose counterregulation and hypoglycemia unawareness, the components of hypoglycemia-associated autonomic failure – analogous to that which develops early in the course of T1DM. Clearly, prevention of hypoglycemia is preferable to its treatment. By practicing hypoglycemia risk reduction – addressing the issue, applying the principles of aggressive glycemic therapy and considering both the conventional risk factors and those indicative of compromised glucose counterregulation – the therapeutic goal is to reduce mean glycemia as much as can be accomplished safely in a given patient at a given stage of T2DM. Particularly in view of the growing array of glucose-lowering drugs that can be used to optimize therapy, hypoglycemia should not be used as an excuse for poor glycemic control. Nonetheless, better methods, such as those that would provide plasma glucose regulated insulin secretion or replacement, are needed for people with T2DM, as well as those with T1DM, if euglycemia is to be maintained over a lifetime of diabetes.

**Key Words:** Hypoglycemia; barrier to glycemic control; therapy with sulfonylureas; therapy with metformin; therapy with insulin; insulin analogues; glucagon; epinephrine; defective glucose counterregulation; hypoglycemia unawareness; hypoglycemia-associated autonomic; failure.

## HYPOGLYCEMIA IN DIABETES: THE CLINICAL PROBLEM

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes *(1–3)*. It causes recurrent morbidity in most people with type 1 diabetes (T1DM) and many with type 2 diabetes (T2DM), and is sometimes fatal. The barrier of hypoglycemia—its reality and its possibility—precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the vascular benefits of glycemic control *(4–6)*. Importantly, episodes of hypoglycemia, even asymptomatic episodes, impair physiological and behavioral defenses against subsequent hypoglycemia by causing hypoglycemia-associated autonomic failure (the clinical syndromes of defective glucose counterregulation and hypoglycemia unawareness) and thus a vicious cycle of recurrent hypoglycemia *(1–3)*.

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Table 1
American Diabetes Association Workgroup on Hypoglycemia recommended classification of hypoglycemia in people with diabetes *(8)*

***Severe Hypoglycemia.*** An episode requiring the assistance of another person to raise the plasma glucose concentration resulting in resolution of symptoms, with or without a measured low plasma glucose concentration.

***Documented Symptomatic Hypoglycemia.*** Symptoms consistent with hypoglycemia with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).

***Asymptomatic Hypoglycemia.*** A measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L) in the absence of symptoms.

***Probable Symptomatic Hypoglycemia.*** Typical symptoms of hypoglycemia without a measured plasma glucose concentration.

***Relative Hypoglycemia.*** Typical symptoms of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (3.9 mmol/L) but approaching that level. (Such episodes occur in people with poorly controlled diabetes.)

Episodes of iatrogenic hypoglycemia cause both physical and psychological morbidity. The physical morbidity ranges from unpleasant neurogenic symptoms (e.g., sweating, hunger, anxiety, palpitations, and tremor) and neuroglycopenic manifestations (e.g. behavioral changes and cognitive impairment) to expressions of severe neuroglycopenia such as seizure and coma. Transient focal neurological deficits sometimes occur. Although seemingly complete neurological recovery is the rule, severe, prolonged hypoglycemia can result in permanent neurological damage, and even death *(7)*. At the very least, an episode of hypoglycemia is a nuisance and a distraction. It can be embarrassing and lead to social ostracism. The additional psychological morbidity includes fear of hypoglycemia, guilt about that rational fear and high levels of anxiety that can be an impediment to glycemic control. The performance of critical tasks, such as driving, is measurably impaired, as is judgement.

Because the glycemic thresholds for the manifestations of hypoglycemia are dynamic—they shift to higher than normal plasma glucose concentrations in poorly controlled diabetes and to lower than normal plasma glucose concentrations in well controlled diabetes, as discussed later—it is not possible to specify a plasma glucose concentration that defines hypoglycemia in people with diabetes. The diagnosis is made most convincingly by documentation of Whipple's Triad: symptoms consistent with hypoglycemia, a low plasma glucose concentration, and relief of those symptoms after the plasma glucose concentration is raised to (or above) normal. Nonetheless, the American Diabetes Association Workgroup on Hypoglycemia *(8)* recommended that people with diabetes should become concerned, and consider defensive actions, at a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L). That plasma glucose level approximates the lower limit of the postabsorptive plasma glucose concentration range and the glycemic threshold for activation of glucose counterregulatory (plasma glucose-raising) systems, as well as the upper level at which an antecedent low plasma glucose concentration results in reduced glucose counterregulatory responses to subsequent hypoglycemia, in nondiabetic individuals. The Workgroup also recommended a classification of hypoglycemia in people with diabetes (Table 1).

On this background of the clinical problem of hypoglycemia in diabetes, the incidence and pathophysiology of, and risk factors for, hypoglycemia in T2DM and clinical approaches to its prevention and treatment are discussed in this chapter. The premises are that iatrogenic hypoglycemia becomes progressively more limiting to glycemic control as patients approach the insulin deficient end of the spectrum of T2DM, that the pathophysiology of glucose counterregulation becomes similar to that in T1DM as patients progress across that spectrum, and that it is possible to both improve glycemic control and reduce the risk of hypoglycemia even in advanced, insulin deficient T2DM, just as it is in T1DM *(1–3)*.

## FREQUENCY OF HYPOGLYCEMIA

During aggressive glycemic therapy, the average patient with T1DM suffers plasma glucose concentrations <50 mg/dL (2.8 mmol/L) approx 10% of the time, symptomatic hypoglycemia about twice a week and severe, at least temporarily disabling, hypoglycemia about once a year *(1)*. Valid estimates of the frequencies of these hypoglycemias (i.e., those based on controlled studies designed to include treatment to near euglycemia) during aggressive glycemic therapy of T2DM are limited *(1)*. Ascertainment of hypoglycemia in T2DM is a

**Table 2**
**Cumulative prevalence of hypoglycemia (percent of patients affected) in T2DM over 6 yr in the United Kingdom Prospective Diabetes Study *(9)***

| *Therapy** | *n* | *$HbA_{1C}$ (%)* | *% with Any* | *Hypoglycemia Major*** |
|---|---|---|---|---|
| Diet | 379 | 8 | 3 | 0.15 |
| Sulfonylurea | 922 | 7.1 | 45 | 3.3 |
| Insulin | 689 | 7.1 | 76 | 11.2*** |
| Diet | 297 | 8.2 | 2.8 | 0.4 |
| Metformin | 251 | 7.4 | 17.6 | 2.4 |

* Taking assigned medication.
** Requiring medical assistance or admission to hospital.
*** Compared with severe hypoglycemia (that requiring the assistance of another individual) in 65% of T1DM over 6.5 yr in the Diabetes Control and Complications Trial.

major challenge. Event rates for asymptomatic hypoglycemia are virtually unknown and those for symptomatic hypoglycemia are undoubtedly minimum estimates. Those for severe hypoglycemia, a memorable event albeit reflecting only a small fraction of the hypoglycemic experience, are most reliable. Overall, however, hypoglycemia is less frequent in T2DM than it is in T1DM. That likely reflects intact defenses against falling plasma glucose concentrations early in the course of the disease, but compromised defenses later.

Iatrogenic hypoglycemia occurs during treatment with a sulfonylurea or insulin, or perhaps with metformin, even in patients with T2DM treated with these drugs from the time of diagnosis. For example, although adjudicated hypoglycemia event rates in the UKPDS have not been published, self-reported data from the United Kingdom Prospective Diabetes Study (UKPDS) *(9)* indicate that, compared with diet alone, therapy with metformin, sulfonylurea or insulin was associated with a 6-fold, 22-fold and 75-fold increased risk, respectively, of the proportion of patients suffering major hypoglycemia over the first 6 yr of diagnosed T2DM (Table 2).

Iatrogenic hypoglycemia becomes a progressively more frequent clinical problem as patients approach the insulin deficient end of the spectrum of T2DM. Insulin secretion decreases progressively *(9)* and hypoglycemia becomes more limiting to glycemic control over time *(10)*. Indeed, in one series, the frequency of severe hypoglycemia was similar in T2DM and T1DM matched for duration of insulin therapy *(11)*. Population-based data indicate that the incidence of hypoglycemia in insulin treated T2DM approaches that in T1DM. For example, data from Tayside, Scotland indicate that the event rates for any hypoglycemia and for severe hypoglycemia in insulin treated T2DM were 38% and 30%, respectively, of those in T1DM *(12)*. Similarly, in insulin treated T2DM the event rates for hypoglycemia requiring emergency treatment in hospital regions of known total and diabetic populations have been reported to be 40% *(13)* or even 100% *(14)* of those in T1DM.

The fact that hypoglycemia becomes a progressively more frequent clinical problem as patients approach the insulin deficient end of the spectrum of T2DM *(9–14)* is explicable on the basis of the pathophysiology of glucose counterregulation in the insulin deficient state.

## PHYSIOLOGY AND PATHOPHYSIOLOGY OF GLUCOSE COUNTERREGULATION

The critical components of the physiology of glucose counterregulation *(15)*—the redundant, hierarchical mechanisms that normally prevent or rapidly correct hypoglycemia—are: 1) A decrease in pancreatic $\beta$-cell insulin secretion that occurs as plasma glucose concentrations decline within the physiological range and favors increased endogenous hepatic (and renal) glucose production and decreased glucose utilization by insulin sensitive tissues such as muscle. 2) An increase in pancreatic $\alpha$-cell glucagon secretion, which occurs as plasma glucose concentrations fall just below the physiological range and stimulates hepatic glucose production. 3) An increase in adrenomedullary epinephrine secretion, which also occurs as plasma glucose concentrations fall just below the physiological range and which both stimulates hepatic (and renal) glucose production and limits glucose utilization by insulin sensitive tissues. Although demonstrably involved, epinephrine is not normally critical; however, it becomes critical when glucagon is deficient.

All 3 of these key defenses against falling plasma glucose concentrations are compromised in insulin deficient (T1DM and advanced T2DM) diabetes *(1–3)*. In such patients, iatrogenic hypoglycemia is the result of the interplay of relative or absolute insulin excess, which must occur occasionally because of the pharmacokinetic imperfections of all insulin replacement regimens, and compromised glucose counterregulation. When endogenous insulin secretion is deficient, as plasma glucose concentrations fall the plasma insulin concentration does not decrease, because it is a function of the absorption and clearance of administered insulin, and glucagon concentrations do not increase. The latter is also likely the result of endogenous insulin deficiency, because a decrease in intraislet insulin, in concert with a fall in plasma glucose, is normally a signal to increase glucagon secretion during hypoglycemia *(16)*. In addition, the increase in plasma epinephrine concentrations as plasma glucose concentrations fall is typically attenuated; the glycemic threshold for sympathoadrenal responses is shifted to lower plasma glucose concentrations. The latter, a critical feature of the pathophysiology of glucose counterregulation, is generally the result of recent antecedent iatrogenic hypoglycemia, although sleep, and to some extent prior exercise, have the same effect *(2,3)*.

In the setting of absent insulin and glucagon responses, an attenuated epinephrine response to falling plasma glucose concentrations causes the clinical syndrome of *defective glucose counterregulation (1–3)*. Affected patients are at 25-fold or greater increased risk for severe iatrogenic hypoglycemia during aggressive glycemic therapy. An attenuated sympathoadrenal response (largely an attenuated sympathetic neural response *(17)*) causes the clinical syndrome of *hypoglycemia unawareness (1–3)*. Affected patients are at about 6-fold increased risk for severe iatrogenic hypoglycemia during aggressive glycemic therapy.

The unifying concept of *hypoglycemia-associated autonomic failure* (HAAF) (Fig. 1) in T1DM *(18)* and advanced T2DM *(19)* posits that recent antecedent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing epinephrine responses to a given level of subsequent hypoglycemia in the setting of absent decrements in insulin and absent increments in glucagon) and hypoglycemia unawareness (by reducing sympathoadrenal and the resulting neurogenic symptom responses to a given level of subsequent hypoglycemia) and thus a vicious cycle of recurrent hypoglycemia *(1–3)*. The concept has been extended to include sleep-related and exercise-related HAAF *(2,3)* (Fig. 1).

The clinical impact of HAAF is well established in T1DM *(1–3)*. Recent antecedent hypoglycemia, even asymptomatic nocturnal hypoglycemia, reduces sympathoadrenal epinephrine and neurogenic symptom responses to subsequent hypoglycemia. It also impairs glycemic defense against hyperinsulinemia and impairs detection of hypoglycemia in the clinical setting. Finally, the finding that as little as 2 to 3 wk of scrupulous avoidance of hypoglycemia reverses hypoglycemia unawareness, and improves the reduced epinephrine component of defective glucose counterregulation, in most affected patients provides compelling support for the concept of HAAF. The clinical impact of HAAF is less well established in T2DM *(1–3)*. However, the glucagon response to hypoglycemia is lost, and the glycemic thresholds for responses are shifted to lower plasma glucose concentration by recent

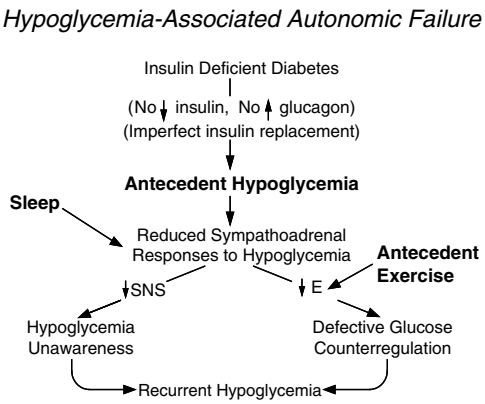


**Fig. 1.** Schematic diagram of the pathophysiology of hypoglycemia-associated autonomic failure in T1DM and advanced T2DM. (Modified from Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. From *(2)*. Copyright 2004, Massachusetts Medical Society, Boston, MA.)

antecedent hypoglycemia, in advanced, i.e., insulin deficient, T2DM *(19)*, as they are in T1DM. Thus, people with T2DM are also at risk for HAAF. This may explain why iatrogenic hypoglycemia becomes more limiting to glycemic control as patients approach the insulin deficient end of the spectrum of T2DM *(9–14)*. In contrast to its clinical impact, the mechanism(s) of HAAF is largely unknown. Possible mechanisms have been reviewed *(3)*.

This pathophysiology of glucose counterregulation in diabetes leads directly to an understanding of the clinical risk factors for iatrogenic hypoglycemia.

## RISK FACTORS FOR HYPOGLYCEMIA

The conventional risk factors for hypoglycemia in diabetes are based on the premise that relative or absolute insulin excess is the sole determinant of risk *(1–3)* (Table 3). Insulin excess occurs when: 1) Insulin (or insulin secretagogue) doses are excessive, ill-timed or of the wrong type. 2) Exogenous glucose delivery is decreased (e.g., following missed meals and during the overnight fast). 3) Endogenous glucose production is decreased (e.g., following alcohol ingestion). 4) Glucose utilization is increased (e.g., during exercise). 5) Sensitivity to insulin is increased (e.g., late after exercise, during the night, following weight loss or improved glycemic control). 6) Insulin clearance is decreased (e.g., with renal failure). These are the risk factors that patients and their care providers must consider when hypoglycemia is recognized to be a problem. However, these conventional risk factors explain only a minority of episodes of iatrogenic hypoglycemia *(20)*.

Iatrogenic hypoglycemia is more appropriately viewed as the result of the interplay of relative or absolute insulin excess and compromised glucose counterregulation in insulin deficient—T1DM and advanced T2DM—diabetes *(1–3)* (Fig. 1). Risk factors indicative of compromised glucose counterregulation (Table 3) (Fig. 1) include: 1) Endogenous insulin deficiency that indicates that insulin levels will not decrease and glucagon levels will not increase as plasma glucose concentrations fall, fundamental features of the clinical syndrome of defective glucose counterregulation. 2) A history of severe hypoglycemia, hypoglycemia unawareness, or both, or aggressive glycemic therapy *per se* (as evidenced by lower $HbA_{1C}$ levels, lower glycemic goals, or both) because these either indicate or imply recent antecedent hypoglycemia. The latter shifts glycemic thresholds for sympathoadrenal responses to lower plasma glucose concentrations and, therefore, reduces the adrenomedullary epinephrine and sympathetic neural responses to a given level of subsequent hypoglycemia. These changes result in the clinical syndromes of defective glucose counterregulation and hypoglycemia unawareness, as discussed earlier. As also mentioned earlier, sleep, and to some extent prior exercise, also reduce sympathoadrenal responses to subsequent hypoglycemia *(2,3)*.

## PREVENTION OF HYPOGLYCEMIA: RISK FACTOR REDUCTION

Clearly, it is preferable to prevent, rather than treat, iatrogenic hypoglycemia. To practice hypoglycemia risk factor reduction *(1)* (Table 4) the provider should: 1) Address the issue of hypoglycemia in every patient contact.

**Table 3**
**Risk factors for iatrogenic hypoglycemia in diabetes**

| |
|---|
| ***Relative or absolute Insulin Excess*** |
| Insulin (or insulin secretagogue) doses that are excessive, ill-timed or of the wrong type |
| Decreased exogenous glucose delivery (missed meals, overnight fast) |
| Decreased exogenous glucose production (drugs including alcohol) |
| Increased glucose utilization (exercise) |
| Increased sensitivity to insulin (late after exercise, during the night, following weight loss or improved glycemic control) |
| Decreased insulin clearance (renal failure) |
| ***Compromised Glucose Counterregulation*** |
| Endogenous insulin deficiency |
| History of severe hypoglycemia, hypoglycemia unawareness, or both |
| Aggressive glycemic therapy per se (lower $HbA_{1C}$, lower glycemic goals, or both) |

Table 4
Hypoglycemia risk reduction

***Address the Issue of Hypoglycemia***
***Apply the Principles of Aggressive Glycemic Therapy***
- Patient education and empowerment
- Frequent self-monitoring blood glucose
- Appropriate and flexible insulin (and other drug) regimens
- Individualized glycemic goals
- Ongoing professional guidance and support

***Consider Both the conventional Risk Factors and Those Indicative of Compromised Glucose Counterregulation*** (Table 3)
- Drug selection and regimen (see text)
- Short-term scrupulous avoidance of hypoglycemia in patients with hypoglycemia-associated autonomic failure

Patients are often reluctant to mention their hypoglycemia, or their fear of hypoglycemia. The problem cannot be solved if it is not acknowledged. 2) Apply the principles of aggressive glycemic therapy – patient education and empowerment, frequent self monitoring of blood glucose, appropriate and flexible insulin (and other drug) regimens, rational individualized glycemic goals, and ongoing professional guidance and support. 3) Consider the conventional risk factors and adjust the regimen accordingly. 4) Consider the possibility of compromised glucose counterregulation and seek a history of hypoglycemia unawareness. Given a history of the latter, a 2–3 wk period of scrupulous avoidance of hypoglycemia is advisable with the expectation that it will reverse hypoglycemia unawareness *(1–3)*.

Drug selection is an important aspect of the prevention of hypoglycemia in T2DM *(1)*. Among the oral hypoglycemic agents, monotherapy with insulin sensitizers such as metformin or the thiazoledinediones should not produce hypoglycemia because those drugs require endogenous insulin secretion, and insulin secretion should decrease as plasma glucose concentrations decline within the physiological range. Nonetheless, as mentioned earlier, metformin has been reported to be associated with hypoglycemia *(9)* (Table 2). Similarly, monotherapy with GLP-1 receptor agonists or DPP-IV inhibitors should not cause hypoglycemia because the incretin-induced increase in insulin secretion is largely, although perhaps not entirely, plasma glucose dependent. Again, insulin secretion should decrease as plasma glucose concentrations decline within the physiological range. However, monotherapy with any of these agents seldom results in long-term glycemic control. To the extent they have some glucose-lowering effect they all can increase the risk of hypoglycemia when combined with administration of an insulin secretagogue or of insulin.

Sulfonylureas, or the nonsulfonylurea insulin secretagogues repaglinide and netaglinide, can produce hypoglycemia. Among the sulfonylureas, glyburide has a more prolonged hypoglycemic action than glimepiride *(21)*, and glyburide is more often associated with clinical hypoglycemia *(22)*. Similarly, the frequency of hypoglycemia appears to be higher with glyburide than with glipizide *(23)*.

Ultimately, most people with T2DM require treatment with insulin to achieve or maintain a degree of glycemic control. Indeed, it could be reasoned that insulin should be introduced earlier, rather than later. Therapy with oral hypoglycemic agents alone can be defended as long as it maintains a level of glycemic control comparable to that which can be achieved by treatment with insulin and does not cause adverse events unique to those agents. Otherwise, avoidance of insulin therapy is not defensible.

Among insulin preparations, insulin analogs are less likely to cause hypoglycemia, at least nocturnal hypoglycemia *(24)*. Those include both long-acting, basal insulin analogs (e.g., glargine or detemir compared with NPH or ultralente) and rapid-acting, prandial insulin analogs (e.g., lispro or aspart compared with regular). A comparison of escalating doses of glargine and of NPH added to oral hypoglycemic agents in patients with T2DM and $HbA_{1C}$ levels >7.5%, resulting in similar $HbA_{1C}$ levels after 24 wk *(25)*, disclosed 2 interesting findings. First, approx 60% of the patients achieved a $HbA_{1C}$ level <7.0%. Thus, a subset of patients, perhaps those with intact glucose counterregulatory systems, can achieve some degree of glycemic control with the addition of a basal insulin alone. Presumably the remaining patients could have achieved that degree of glycemic

control with the addition of prandial insulin. Second, overall hypoglycemia rates were significantly lower with glargine. All symptomatic hypoglycemic episodes were reduced by 21% and those with measured plasma glucose concentrations <56 mg/dL (3.1 mmol/L) were reduced by 41%. Symptomatic nocturnal hypoglycemic episodes were reduced by 42%, and those with measured plasma glucose concentrations <56 mg/dL (3.1 mmol/L) were reduced by 48%. Nonetheless, there were a few more episodes of severe hypoglycemia in the patients treated with glargine (14 in 2.5% of the patients compared with 9 in 1.8% of the patients treated with NPH). A meta-analysis of studies comparing glargine and NPH insulins in T2DM *(26)* indicated that approximately one-third of patients achieved $HbA_{1C}$ levels <7.0% and that episodes of all symptomatic (–11%), nocturnal (–26%), severe (–46%) and severe nocturnal (–59%) hypoglycemia were less frequent in the patients treated with glargine. Again, the goal of reducing $HbA_{1C}$ levels only to <7.0% is a compromise based in the reality of the barrier of hypoglycemia. Ideally, the goal should be a nondiabetic $HbA_{1C}$ level.

Because of its dosing flexibility, continuous subcutaneous insulin infusion (CSII) should be superior to a basal-preprandial bolus (multiple daily injection) insulin regimen. However, compelling evidence is lacking. For example, in a crossover study involving 100 patients with T1DM, nocturnal hypoglycemia event rates were 25% lower, but daytime hypoglycemia event rates were 37% higher, during CSII with an analog (aspart) than during a basal-preprandial bolus regimen with analogs (glargine and aspart) *(27)*. In a randomized trial involving 107 patients with T2DM treated over 1 yr to mean $HbA_{1C}$ levels of ~6.5% with a CSII (lispro) or basal-bolus (glargine and lispro) regimen, there were no significant differences in the rates of self-treated asymptomatic or symptomatic hypoglycemia or in the rates of severe hypoglycemia *(28)*.

Bedtime snacks are the traditional approach to the prevention of nocturnal hypoglycemia. However, their efficacy has been questioned; it appears that they only shift episodes of hypoglycemia to later during the night *(29)*. Experimental approaches to the problem include attempts to produce sustained exogenous glucose delivery throughout the night, with bedtime oral administration of the slowly digested carbohydrate uncooked cornstarch or dinner time administration of an a-glucosidase inhibitor to delay carbohydrate digestion, or to produce sustained endogenous glucose production throughout the night, with bedtime administration of the glucagon stimulating amino acid alanine or the epinephrine simulating $\beta_2$-adrenergic agonist terbutaline *(29,30)*. The latter has been shown to prevent nocturnal hypoglycemia in aggressively treated T1DM *(29)*, but in the dose used it also raised plasma glucose concentrations the following morning.

## TREATMENT OF HYPOGLYCEMIA

Episodes of asymptomatic hypoglycemia and the vast majority of episodes of mild-moderate symptomatic hypoglycemia are self-treated with oral carbohydrates—glucose tablets or candy, beverages or food (Table 5). A dose of 20 g is appropriate *(30)*. The initial increase in the plasma glucose concentration occurs in about 15 min, the maximum increase in about 30 min. The effect lasts only about 2 h. Therefore, the patient should monitor the plasma glucose level and eat a more substantial snack or meal after the glucose level is raised.

Severe hypoglycemia—that requiring the assistance of another person—can also be treated with oral carbohydrates if that is practical. However, parenteral therapy is necessary if the patient is unable or unwilling (because of

**Table 5**
**Treatment of a hypoglycemic episode**

***Oral Carbohydrates*** (20 g)
- Transient increase in plasma glucose (~2 h)
- Monitor glucose levels
- Snack or meal after glucose levels are raised

***Parenteral Therapies:*** *Glucagon* (1.0 mg, 15 μg/kg in children, subcutaneously or intramuscularly) may be less effective in T2DM. *Glucose* (25 g intravenously).
- Monitor glucose levels
- Infuse glucose intravenously as necessary
- Snack or meal after glucose levels are raised

Table 6
Grades of recommendations for key treatment points

| | |
|---|---|
| 1A* | Iatrogenic hypoglycemia can be caused by treatment with insulin, a sulfonylurea, or repaglinide or nateglinide. |
| 1B** | Metformin might cause hypoglycemia. |
| 1A* | Insulin analogues are less likely to cause hypoglycemia, at least nocturnal hypoglycemia. |
| 1C*** | Given a history of hypoglycemia unawareness, a 2–3 wk period of scrupulous avoidance of hypoglycemia is advisable. |

* Clear risk/benefit, randomized trials without important limitations
** Clear risk/benefit, randomized trial with important limitations
*** Clear risk/benefit, observational studies

neuroglycopenia) to take carbohydrates orally. Glucagon, 1.0 mg (15 μg/kg in children), can be injected subcutaneously or intramuscularly by nonmedical individuals such as a spouse, a parent or an associate; it can also be injected intravenously by medical personnel. In T1DM, the glucose-raising effect lasts about 3 h *(30)*. However, because it also stimulates insulin secretion in patients with residual $\beta$-cell function, glucagon is less effective in T2DM. The standard glucagon dose can cause vomiting. Smaller doses, repeated if necessary, have been used to avoid vomiting in children *(31)*. Parenteral, as well as oral, terbutaline also raises plasma glucose concentrations in people with insulin deficient diabetes *(30)*, but its use in T2DM has not been assessed. It might well be that it, like glucagon, would be less effective in patients with residual $\beta$-cell function. Clearly, the preferable parenteral treatment is intravenous glucose. The standard dose is 25 g initially in adults. The plasma glucose concentration should be monitored serially, glucose infused as necessary and a snack or meal provided as soon as that is practical. The duration of a hypoglycemic episode is a function of the pharmacodynamics of the drug that induced it. Episodes caused by a sulfonylurea are often prolonged and require prolonged observation and therapy.

## PERSPECTIVE

Given the steady progress in the glycemic management of diabetes, including the growing array of plasma glucose lowering drugs that can be used to optimize therapy, the barrier of hypoglycemia—its possibility and its reality—should not be used as an excuse for poor glycemic control in people with diabetes. The benefits of near euglycemia, i.e., partial glycemic control, are well established *(4–6)*. Nonetheless, the benefits of a lifetime of euglycemia would undoubtedly be greater. Clearly, better methods, such as those that would provide plasma glucose regulated insulin secretion or replacement, are needed for people with T2DM, as well as those with T1DM, if the goal of long-term euglycemia is to be achieved.

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# 14 Type 2 Diabetes and Concomitant Illness

*The Prepared Practice*

*Kathleen Dungan, Elizabeth Harris, and Susan S. Braithwaite*

***CONTENTS***



**Summary**

Prospective randomized trials have established the importance of glycemic control for the patient with type 2 diabetes with respect to both the outcomes of critical illness treated in the hospital and chronic microvascular complications of diabetes. For other conditions initially recognized in the ambulatory setting, the caregiver is called upon to determine not only whether intensification of antihyperglycemic management is required, but also within what timeframe it must be achieved, and in what setting care will be conducted. Despite the paucity of data on the potential importance of strict glycemic control to concomitant ambulatory conditions other than the classic tissue complications of diabetes, we will attempt to review those conditions for which some evidence exists on the following questions: Does risk of development of the condition correlate with the presence of diabetes? Does risk of development of the condition correlate with glycemic control? Do outcomes of the condition correlate with glycemic control? Do outcomes of the condition correlate with the presence of diabetes? Does the co-morbidity itself affect diabetic control or risk of developing diabetes? Strategies for outpatient care during intercurrent illness are suggested, with remarks about preadmission and postdischarge hospital care.

**Key Words:** Hyperglycemia; ambulatory care; type 2 diabetes; infectious diseases; malignancy; endocrinopathy; insulin therapy.

## HYPERGLYCEMIA AND CONCOMITANT ILLNESSES IN AMBULATORY MEDICINE

### *Introduction*

In the management of stable ambulatory patients having type 2 diabetes, the established targets for glycemic control are based on the evidence from clinical trials in both type 2 and type 1 diabetes regarding risk for microvascular disease in relation to glycemic control *(1–11)*. For patients with type 2 diabetes whose blood glucose is not critically elevated, the timeframe for intensification of antihyperglycemic therapy to achieve these targets usually spans months or years. The need for intensification of treatment is progressive, the approach is nonemergent, and commonly there is failure to attain or maintain target range control *(1,2,12–16)*.

Although published guidelines address management of diabetes-associated comorbidities such as hypertension, dyslipidemia, cardiovascular disease, and microvascular complications *(11)*, in the ambulatory setting practitioners treat many additional comorbidities. Although there is a paucity of established literature on appropriate glycemic

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management, it is likely that benefits accruing from intensification of glycemic control have not been fully realized under present day practice patterns, nor have these putative benefits been adequately studied either on general hospital wards or in the ambulatory setting. It is the goal of this chapter to outline the rationale for aggressive recommendations concerning glycemic management during the evolution of certain ambulatory comorbidities in the presence of type 2 diabetes.

## *Mechanisms of Destabilization of Glycemic Control during Concomitant Illness*

Under normal conditions, insulin works through the insulin receptor and signaling cascades to balance glucose production and peripheral glucose utilization. In patients with type 2 diabetes, as hyperglycemia fails to suppress hepatic glucose production and peripheral glucose uptake declines, this balance is lost *(17)*.

Most of the data on metabolic and hormonal responses to hyperglycemia in animals and humans has been obtained from experimental studies using clamp techniques *(18–20)*. During acute illness or injuries as listed in Table 1, physiologic counter regulatory hormone and cytokine responses are abnormal in patients with underlying inflammatory and metabolic abnormalities such as type 2 diabetes *(21,22)*. Acute illness is characterized by a hypercatabolic state with relative insulin deficiency, increase of catecholamines, and stimulation by tumor necrosis factor-α (TNF-α) of lipolysis, resulting in increased plasma free fatty acids. Proinflammatory cytokines including TNF-α and interleukin (IL) 6 increase in both acute and chronic stress-related conditions. In cultured murine adipocytes, elevation of TNF-α interferes with insulin signaling through the insulin receptor *(23)*. Downstream of the insulin receptor, serine phosphorylation (pS) of insulin receptor substrate (IRS) molecules prevents tyrosine phosphorylation (pY) of IRS, thus blocking normal insulin action in murine hepatocytes *(24)*. The result is lipolysis with release of free fatty acids (FFA) from adipocytes. It is hypothesized that a cycle ensues with TNF-a induction of lipolysis and release of FFA from adipocytes, causing insulin resistance in muscle, liver, and adipocytes and further release of FFAs *(25)*.

Free fatty acids dose dependently cause insulin resistance in skeletal muscle and liver *(26)*. In human skeletal muscle, FFAs inhibit insulin-stimulated glucose uptake through inhibition of glucose transport with diminished phosphorylation activity *(27)*. In rat hepatic tissue, FFAs increase activity of PKC-delta *(26,28)*. FFAs also increase activation of the proinflammatory NFkB pathway and increase expression of inflammatory cytokines including TNF-α in hepatic rat tissue *(26)*. The induction of hepatic insulin resistance leads to hyperglycemia and contributes to the perpetuation of the inflammatory response *(26)*.

## *Mechanisms of Harm during Hyperglycemia and Benefit from Glycemic Control*

Improving glycemic control in the surgical and medical intensive care unit has been shown to improve outcomes *(22,29–41)*. Van den Berghe treated hyperglycemia with insulin in the acute intensive care setting and demonstrated reduction of mortality and morbidity even in patients without apparent diabetes. While 99% of the intensive therapy group ($n$ = 765) and 39% of the control group ($n$ = 783) received intravenous insulin infusion in the trial of Van den Berghe and colleagues, the difference in blood glucose levels was only 50 mg/dL. Among patients treated in the DIGAMI I trial for myocardial infarction and Portland coronary artery bypass surgery studies, the survival advantage during intensive glycemic management was attributed largely to reduction in death owing to arrhythmia, pump failure, and reinfarction *(30,34)*, whereas among patient in the Leuven, Belgium studies of glycemic control in the surgical ICU the improvement in mortality rate was owing to a reduction of septic

**Table 1**
**Factors contributing to destabilization of glycemic control during intercurrent illness**

| |
|---|
| Altered caloric and carbohydrate exposure |
| Altered physical activity |
| Drugs |
| Organ dysfunction |
| Trauma |
| Infection |
| Inflammation |

**Table 2**
**Putative physiologic and tissue targets for protection with effective insulin therapy used to control hyperglycemia during critical illness**

- Coagulation pathway
- Inflammatory pathway
  - Proinflammatory transcription factors
  - Gene products
    (a) Adhesion molecules (ICAM-1, E-selectin)
    (b) Matrix metalloproteinases
    (c) PAI-1
    (d) Other
- Hepatic iNOS, plasma NO metabolites
- Endothelium
  - Vessel wall inflammatory processes
  - Vasomotor tone
- Heart
- Host defenses against infection
- Fuel and energy metabolism
  - Glucose
  - Free fatty acids
  - Reactive oxygen species
  - Nutritional status
- Fluid and electrolyte balance

deaths *(29)*. The reduction of morbidities included duration of ventilator dependency, transfusion requirement, acute renal failure, and unit neuropathy. Although the mechanism by which insulin improves outcomes is still not well defined, it is thought to involve both metabolic effects of lowering blood glucose as well as direct effects of insulin on inflammatory cytokines, nitric oxide, free fatty acids, and transcription of glucose transporters *(25,42)*.

In Table 2, the target pathways, tissues, and pathogenetic mechanisms suspected to be important among critically ill patients, and possibly benefited by intensive intravenous insulin therapy, are listed. Speculative pathways of injury focus on endothelial function and include concepts that also are proposed as mechanisms contributory to macrovascular disease. Ambulatory patients having infectious diseases and other concomitant conditions at some point cross a threshold of severity of illness such that some of these putative "inpatient" mechanisms of injury might apply during evolution of outpatient illness and become operative before admission to a hospital. Cardiac function, host defenses against infection, fuel and energy metabolism, and fluid and electrolyte balance are at risk in both the inpatient and the ambulatory setting. In fact, blood glucose upon admission may be a prognostic indicator for the outcome of hospitalization *(43–49)*.

## Coagulation, the Inflammatory Pathway, Nitric Oxide, and the Endothelium

TNF-α is implicated in inflammation, cell apoptosis and survival, cytotoxicity, production of IL-1 and IL-6, and induction of insulin resistance in numerous clinical settings *(50)*. Proinflammatory cytokines such as TNF-α stimulate corticotrophin-releasing hormone, with eventual elevation in cortisol *(51)*. In addition to inducing hyperglycemia and insulin resistance, glucocorticoids exert an anti-inflammatory effect through reduction of the proinflammatory transcription factor NFkB preventing initiation of the inflammatory process. Insulin has been shown to have similar anti-inflammatory effects at the cellular and molecular level. Insulin infusions in mononuclear cells of obese nondiabetic subjects reduce NFkB, subsequent transcription of proinflammatory cytokines, adhesion molecules and enzymatic mechanisms that cause ROS generation *(52)*. Despite marked differences in glycemic response, corticosteroids and insulin have similar anti-inflammatory effects.

Insulin has a direct effect on nitric oxide synthesis from vascular endothelium through its effects on nitric oxide synthase (eNOS) *(53–55)*. The eNOS gene transcription and activity are upregulated by insulin. Nitric oxide generated by eNOS causes vasodilation and antiaggregation effect on platelets *(56,57)*. Thus, it is not

surprising that nitric oxide increases blood flow to the upper and lower extremities as well as cause dilation of the carotid artery *(54,58,59)*.

An hepatic isoform of nitric oxide synthetase, iNOS, can generate higher levels of circulating nitric oxide concentrations that can be proinflammatory and evoke organ damage in ischemia *(60)*. In a large, randomized controlled study using intensive insulin in critically ill patients, prevention of hyperglycemia with intensive insulin therapy suppressed iNOS gene expression and lowered circulating nitric oxide levels. The authors concluded that these effects on the endothelium statistically explained a significant part of the improved patient outcome with insulin therapy *(60)*.

### Host Defenses against Infection

A number of observational studies and postinterventional comparisons to historical series support the concept that among hospitalized patients infection is less likely to occur or progress with stringent glycemic control *(33,38,47,61–64)*. There is impaired neutrophil function in the presence of hyperglycemia, with evidence from some studies suggesting reversibility upon correction of hyperglycemia and with the use of insulin *(65–71)*. Host defense against mucormycosis is reduced in diabetes, especially in the presence of acidosis *(72,73)*.

### Nutrition, Flux of Metabolites, Hydration, and Electrolyte Status

Increased free fatty acids have been shown in a prospective long term study to be an independent risk factor for sudden death *(74)*. Increasing concentrations of free fatty acids cause endothelial dysfunction in a dose-dependent relationship in healthy, nonobese subjects *(55)* and are arrhythmogenic. Although insulin is known to inhibit free fatty acids, the changes in insulin-induced free fatty acid suppression with insulin treatment in different degrees of illness have not been studied *(50)*. In the setting of hyperglycemic hyperosmolar state, the severity of hyperglycemia and dehydration on admission are important prognostic indicators, along with the nature and severity of the underlying inciting illness *(75–84)*.

## *Populations at Risk*

### Elderly

The geriatric population is at risk for complications of diabetes during acute illness. With increasing age, insulin secretory reserve, insulin sensitivity, and thirst mechanisms decrease. Thus, infection and illness make the elderly patient particularly vulnerable to hyperglycemia and dehydration *(84)*. Diabetic hyperosmolar state is defined by serum glucose greater than 600 mg/dL and serum osmolarity greater than 320 Osm/L. Increasing age, nursing home residence, and infection are predisposing factors, and mortality figures are reported as 10 to 20%. In addition, increasing age and associated illness are also risk factors for increased mortality in diabetic hyperosmolar state *(75–84)*.

### Socioeconomically Disadvantaged

Low-income patients are also at increased risk for complications during acute illness. A cross-sectional analysis of administrative claims over 2 yr of 9,453 patients aged 65–75 yr demonstrated that Medicare/Medicaid status was independently associated with not receiving diabetes care, including annual HgbA1C, biennial eye exam, and biennial lipid testing. Membership in a minority race and increased visits to the emergency department were significantly associated with lack of diabetes care in the Medicare/Medicaid population, and adverse outcomes in minority populations, although multifactorial, may hinge in part on access to health care resources *(85–89)*.

A population-based cohort study of 600,000 diabetic patients in Canada demonstrated that individuals in the lowest income quintile were 44% more likely than those in the highest income quintile to have one or more hospitalizations or emergency department visits for hyperglycemia or hypoglycemia. This relationship existed after adjusting for age, sex, urban versus rural residence, comorbidity, frequency of physician visits, continuity of care, physician specialty, and geographic region. Reasons for admission that were not amenable to outpatient care, including appendicitis and hip fracture, were not affected by socioeconomic status. Even when diabetic patients have access to health care, lower socioeconomic status is associated with increased number of acute visits for causes that might be avoided by optimal ambulatory care *(90)*.

## SPECIFIC INTERCURRENT CONDITIONS IN THE AMBULATORY SETTING

Diabetes is associated with higher risk for many illnesses. In some cases, this risk may be related to glycemic control. Although hyperglycemia may increase the likelihood of illness, the illness itself may also lead to hyperglycemia. Perhaps causality can be inferred by measuring HbA1c. In addition, there is evidence that many illnesses have worse outcomes in the presence of diabetes and this finding may also be related to glycemic control. There is increasing data that establishing normoglycemia will improve outcomes, particularly in the intensive care unit, but this has not yet been vigorously studied in outpatients. In the outpatient setting there is little data from randomized, prospectively conducted studies to demonstrate the directionality of the role of hyperglycemia with respect to causation of many illnesses. Much of the evidence relies on observational or epidemiological studies. A discussion of the relationship between diabetes and glycemic control follows, with a discussion of evidence that may suggest impact upon the incidence and severity of various intercurrent illnesses and how those illnesses may, in turn, affect glycemic control.

### *Infection*

#### General Comments on Infection

The problem of infection and diabetes has been comprehensively studied and reviewed *(91–98)*. Progression of infectious illnesses and, for some specific infectious disorders, the initial occurrence of the infection probably should be added to the list of diabetes complications *(3,92,93,97–172)*. Several studies have determined that the incidence of overall infection is increased in patients with diabetes, as shown in Table 3 *(96–98)*. A prospective cohort study included 6,712 patients with type 2 diabetes *(98)*. Compared to hypertensive controls, the incidence of infections and the risk for recurrence was equal to or greater in those with diabetes. Infection with specific microorganisms such as *Klebsiella*, *Staphylococcus aureus*, *Salmonella enteritidiis*, *Candida*, and *Mycobacterium tuberculosis*, and specific uncommon infections such as endophthalmitis or liver abscess, are strongly associated with diabetes; these problems have been reviewed elsewhere *(93,94,100)*.

The risk of any infection may be related to glycemic control (Table 4). In the outpatient setting, prospectively randomized trials for the impact of glycemic control upon specific infections have not been conducted. However, in a retrospective study, Rayfield and colleagues reviewed the charts of 241 patients with diabetes in an outpatient setting *(92)*. There were 282 infections documented in 114 patients. There was a significant correlation ( $p < 0.001$) between mean plasma glucose and the overall incidence of infection. This was not associated with patient age, type of therapy, duration of diabetes, or comorbidities. The relationship of hyperglycemia to infection was assumed to be causal rather than a marker of acute illness because glucose levels were obtained on occasions when no suspicion of infection existed. A prospective observational matched-pair cohort analysis *(97)* did not find an association with HbA1c, although the narrow range of HbA1cs among subjects (median HbA1c 7.4%, range 6.6–8.2%) may have precluded such an analysis. Patients developed 79% more infections overall, but this was a result of multiple episodes in affected patients rather than an increase in overall risk.

In many instances, patients with diabetes have worse outcomes overall (Table 5). NHANES II *(95)* examined 533 adults with diabetes and 8,675 without diabetes. Over 12–16 yr, there were 301 deaths related to infection. Patients with diabetes were at higher risk compared to controls for all-cause and infection-related mortality (age-adjusted RR 1.9, 95%CI 1.5–2.3 and RR 2.4, 95%CI 1.2–4.7 for women respectively and RR 1.7, 95%CI 1.4–2.1 and RR 1.7, 95%CI 0.8–4.7 for men respectively). In addition, a retrospective Ontario cohort of 513,749 patients with diabetes found an increased relative risk for infectious disease hospitalization (RR1.21, 99% CI 1.20–1.22) *(96)*. In particular, the risk for admission with sepsis, postoperative infections, biliary tree infections, and peritonitis was increased in the presence of diabetes *(96)*. Furthermore, the risk for admission was greater for a large number of specific infections that sometimes are treated in the ambulatory setting, including upper respiratory tract infections, cystitis, pneumonia, cellulitis, enteric infections, otitis externa, mycoses, genital infections, herpes zoster, viral hepatitis, pyelonephritis, tuberculosis, osteomyelitis, mononucleosis, rectal abscess, and infectious arthritis *(96)*. There was a significantly increased rate of death attributable to infectious disease (1.0% vs. 0.6% of age-matched controls). However, applying this data to the outpatient setting may be complicated, as a subset of patients was obtained from hospital records.

Table 3
Association of infectious diseases with diabetes or hyperglycemia

| | | *Increased risk for developing conditions* |
|---|---|---|
| Any infection | Shah 2003 *(96)* | RR 1.21 (1.20–1.22) |
| | Davis 2005 *(97)* | 75 infections in patients with DM vs. 42 in controls ( $p = 0.0005$) |
| Bacteremia | Bryan 1985 *(101)* | 19.4/1000 in DM vs. 9.4/1000 in controls ( $p < 0.0001$) |
| | MacFarlane 1986 *(99)* | DM present in 29.2% of bacteremic patients vs. 10% of general hospital population ( $p < 0.001$) |
| Pneumococcal bacteremia | Thomsen 2004 *(102, 103)* | OR 1.9 (1.4–2.6) |
| Otitis externa | Doroghazi 1981 *(105)* | DM present in 115/129 patients (89%) in literature search |
| | Shah 2003 *(96)* | RR 1.14 (1.09–1.18) |
| Invasive fungal sinusitis | Blitzer 1980 *(104)* | DM present in 126/179 patients (79%) |
| | Sohail 2001 *(106)* | DM present in 5/9 patients (55.6%) |
| | Parikh 2004 *(107)* | DM present in 10/45 patients (22%) |
| | Hosseini 2005 *(108)* | DM present in 9/10 patients (90%) |
| | Shah 2003 *(96)* | RR 1.38 (1.32–1.44) |
| Periodontal disease | Khader 2006 *(113)* | Plaque index $D = 0.218$ (0.098–0.33, $p = 0.003$), Gingival index $D = 0.147$ (0.012–0.281, $p = 0.331$), Probing pocket depth $D = 0.346$ (0.194–0.498, $p < 0.0001$), clinical attachment loss $D = 0.612$ (0.462–0.761, $p < 0.001$); Plaque index, bleeding to probing and plaque extent NS |
| Upper respiratory tract infection | Shah 2003 *(96)* | RR 1.18 (1.17–1.19) |
| | Muller 2005 *(98)* | T1DM: adjusted OR 0.95 (0.72–1.26); T2DM: adjusted OR 1.05 (0.95–1.18) |
| Pneumonia | Shah 2003 *(96)* | RR 1.46 (1.42–1.49) |
| | Muller 2005 *(98)* | T1DM: adjusted OR 1.42 (0.96–2.08); T2DM: adjusted OR 1.32 (1.13–1.53) |
| Tuberculosis | Shah 2003 *(96)* | RR 1.12 (1.03–1.23) |
| Enteric infection | Shah 2003 *(96)* | RR 1.50 (1.46–1.54) |
| Viral hepatitis | Zein 2005 *(129)* | HCV: 14.5% with DM vs. 7.8% without DM ( $p = 0.0008$) |
| | Kwon 2005 *(128)* | HCV: 43.2% with DM vs. HBV: 19.7% with DM ( $p < 0.00001$) |
| | Shah 2003 *(96)* | RR 1.49 (1.39–1.60) |
| Biliary infections | Edinburgh 1958 *(130)* | Emphysematous cholecystitis: 12/50 patients (24%) with DM |
| | Garcia-Sancho Tellez 1999 *(131)* | Emphysematous cholecystitis: 11/20 patients (55%) with DM |
| | Shah 2003 *(96)* | RR 1.60 (1.39–1.83) |
| Peritonitis | Shah 2003 *(96)* | RR 1.94 (1.58–2.37) |
| | Chow 2005 *(144)* | Median peritonitis free time 49.0 vs. 82.3 mo in DM vs. no DM ( $p = 0.0019$) |
| UTI | Boyko 2002 *(134)* | OR 2.2 (1.6–3.0) |
| | Shah 2003 *(96)* | RR 1.39 (1.36–1.42) |
| | Hu 2004 *(137)* | OR 2.78 (1.78–4.35) |
| | Boyko 2005 *(138)* | RR 1.8 (1.2–2.7) |
| | Muller 2005 *(98)* | T1DM: adjusted OR 1.96 (1.49–2.58); T2DM: adjusted OR 1.24 (1.10–1.39) |
| Pyelonephritis | Scholes 2005 *(139)* | OR 4.1 (1.6–10.9) |
| | Shah 2003 *(96)* | RR 1.95 (1.78–2.13) |

(*Continued*)

**Table 3**
**(*Continued*)**

| | | *Increased risk for developing conditions* |
|---|---|---|
| Emphysematous pyelonephritis or cystitis | Wan 1998 *(142)* | 37/38 patients (97%) with DM |
| | Shah 2003 *(96)* | RR 1.95 (1.78–2.13) |
| GU infection | Shah 2003 *(96)* | Males: RR 0.89 (0.86–0.89); Females: RR 1.16 (1.04–1.30) |
| Dermatophytosis | Lugo-Somolinos 1992 *(145)* | Present in 31/100 patients (31%) with DM vs. 33/100 (33%) without DM |
| | Muller 2005 *(98)* | T1DM: adjusted OR 1.34 (0.97–1.84); T2DM: adjusted OR 1.44 (1.27–1.63) |
| | Romano 2001 *(148)* | 7/171 patients (4.1%) with DM vs. 17/276 ( 6.1%) without DM |
| Necrotizing fasciitis | Pessa 1985 *(150)* | 8/30 patients (26.7%) with DM |
| | Gozal 1986 *(151)* | 5/13 patients (38.5%) with DM |
| | Nisbet 2002 *(153)* | 20/26 patients (76.9%) with DM |
| | Yeniyol 2004 *(155)* | 18/25 patients (72%) with DM |
| | Korkut 2003 *(154)* | 25/45 patients (55.6%) with DM |
| Cellulitis | Muller 2005 *(98)* | T1DM: adjusted OR 1.59 (1.12–2.24); T2DM: adjusted OR 1.33 (1.15–1.54) |
| | Shah 2003 *(96)* | RR 1.81 (1.76–1.86) |
| Foot ulcers | Currie 1998 *(158)* | OR 7.6 (6.84–8.92) |
| | Leibovici 1996 *(93)* | 9/132 patients (6.8%) with DM vs. 1/383 (2.6%) without DM ( $p = 0.003$) |
| | Walters 1992 *(157)* | OR 2.94 (1.58–5.48) |
| Osteomyelitis | Shah 2003 *(96)* | RR 4.93 ( (3.8–5.06) |
| Discitis | Friedman 2002 *(167)* | 11/29 patients (37.9%) had DM |
| | Faella 2002 *(168)* | 4/17 patients (23.5%) had DM |
| | Mann 2004 *(169)* | 20/26 patients (76.9%) had DM |
| Septic Arthritis | Kaandorp 1995 *(170)* | OR 3.3 (1.1–10.1) |
| | Shah 2003 *(96)* | RR 1.72 (1.42–2.08) |
| Bacterial Meningitis | Huang 2002 *(172)* | 47/122 patients (38%) had DM |
| | Durand 1993 *(171)* | 10/253 patients (4.0%) had DM |
| | Shah 2003 *(96)* | RR 1.50 (1.46–1.54) |

Where available, risk ratios are followed by confidence intervals in parentheses. Confidence intervals are 95% confidence intervals except for Shah et al. *(96)* which reported 99% confidence intervals. Absolute values are followed by measures of statistical significance ( $p$-values) in parentheses where available. NS, nonsignificant; RR, relative risk; OR, odds ratio.

One study suggests that worse outcomes may be associated with worse baseline glycemic control *(93)*. Among 132 inpatients (26% of the total population studied), diabetes was not an independent predictor of mortality except in patients with a glycated hemoglobin (GHb) above the median, 10.3% (OR 3.3, 95% CI 1.8–6.2). Table 6 describes several studies that examined the role of glycemic control in infectious disease occurrence or outcome.

Conversely, infection may affect glycemic control. It is the most common precipitant of diabetic ketoacidosis and nonketotic hyperosmolar state, and infection is an independent predictor for survival in nonketotic hyperosmolar state *(78–81)*.

The incidence and outcomes of infection among patients with diabetes may depend on the anatomical site and the pathogen in question. Selected examples are discussed below.

### Invasive Fungal Sinusitis

Invasive fungal sinusitis is associated with diabetes, and commonly presents in patients with poor glycemic control *(106,108)*. It is unclear whether patients with diabetes have higher morbidity or mortality *(104,107)*. This may depend in part on index of suspicion and rapidity of diagnosis *(107)*.

Table 4
Association of infectious diseases with glycemic control

| | | *Risk for developing conditions associated with glycemic control* |
|---|---|---|
| Any infection | Rayfield 1982 *(92)* | Mean fasting blood glucose prospectively correlated with infection occurrence ( $p < 0.001$, $r^2$ not given) |
| | Davis 2005 *(97)* | A1c 7.1% in patients with infection vs. 7.8% without infection, $p =$ NS |
| Otitis externa | Doroghazi 1981 *(105)* | 3/15 patients (20%) had worsened glucose control (increased insulin requirement or new 3–4+ glucosuria) |
| Invasive fungal sinusitis | Hosseini 2005 *(108)* | 4/9 patients (44%) with DM presented with diabetic ketoacidosis |
| | Sohail 2001 *(106)* | 4/5 patients (80%) with DM presented with diabetic ketoacidosis |
| UTI | Zhanel 1995 *(132)* | A1c 10.9% in patients with bacteruria vs. 13.3% if no bacteruria ( $p =$ NS) |
| | Geerlings 2001 *(133)* | T1DM: UTI A1c 8.6% vs. no UTI 8.3% ( $p =$ NS); T2DM: UTI A1c 8.6% vs. no UTI 8.5% ( $p =$ NS) |
| | Boyko 2002 *(134)* | A1c for DM + UTI 10.3% vs. DM + no UTI 10.0% ( $p =$ NS) Multivariate OR for patients with DM and A1c $>$ 8.0% 2.7 (1.5–4.9) Multivariate OR for patients with DM and A1c $<$ 8.0% 2.4 (1.3–4.5) |
| | Boyko 2005 *(138)* | All ranges of A1c (including $>$ 8.5%) NS except for A1c $>$ 7.9%: incidence ratio 2.7 (1.4–4.7) |
| Emphysematous pyelonephritis or cystitis | Wan 1998 *(142)* | Mean glucose for survivors 357.35 vs. nonsurvivors 472.5 mg/dL |
| Dermatophytosis | Romano 1998, 2001 *(147,148)* | A1c 8.8% for patients with skin infections vs. 8..1% for controls ( $p < 0.01$); Dermatophytosis or candidiasis accounted for 81% of total skin infections |
| | Romano 2001 *(148)* | No association with A1c or glucose |
| | Gupta 2005 *(149)* | Mean A1c over previous 3 yr did not predict occurrence (data not shown) |
| Oral candidiasis | Hill 1989 *(146)* | OR 13 (2.52–67.19) for A1c $>$ 12% |
| Bacterial meningitis | Durand 1993 *(171)* | 11/47 patients (23%) with DM had diabetic ketoacidosis or hyperglycemic hyperosmoloar nonketotic syndrome |

Where available, risk ratios are followed by confidence intervals in parentheses. Confidence intervals are 95% confidence intervals except for Shah et al *(295)*, which reported 99% confidence intervals. Absolute values are followed by measures of statistical significance ( $p$-values) in parentheses where available. RR, relative risk; OR, odds ratio; NS, nonsignificant.

## Periodontitis

There may be a relationship between periodontal disease and diabetes, but there are few prospective trials. A meta-analysis included 21 observational studies and 2 clinical trials, including 4 that examined type 2 diabetes and 6 that examined a mixed population of type 1 and type 2 diabetes *(113)*. Patients with diabetes had a higher severity of gingival and periodontal disease but similar extent of involvement as those without diabetes. The study could not confirm a significant causative effect of poor glycemic control on severity of disease. Conversely, there is also evidence that the presence of periodontal disease may affect glycemic control. In a study of 113 Pima Indians with severe periodontal disease and poorly controlled diabetes, treatment with Doxycycline and topical antimicrobials was associated with a 0.5% to 0.94% reduction in HbA1c ($p < 0.04$) compared to placebo *(110)*. Complications of dental infections may manifest as deep neck infection. Chen et al performed a retrospective

**Table 5**
**Infectious diseases and diseases complicated by infection for which diabetes may worsen outcomes**

| | | *Outcomes related to presence of diabetes* |
|---|---|---|
| Any infection | Bertoni 2001 *(95)* | RR 2.0 (1.2–3.2) |
| | Shah 2003 *(96)* | RR 1.92 (1.79–2.05) |
| Bacteremia | Bryan 1985 *(101)* | 6.4/1000 for DM vs. 2.8/1000 for control ($p < 0.001$) |
| | MacFarlane 1986 *(99)* | Mortality in 10/49 patients (20%) with DM vs. 41/119 (34%) with DM ($p =$ NS) |
| | Leibovici 1991 *(100)* | Septic shock in 14% patients with DM vs. 7% without DM ($p = 0.01$) but mortality in 28% with DM, 29% without ($p =$ NS) |
| | Thomsen 2004 *(102, 103)* | Mortality rate ratio 0.6 (0.3–1.2) |
| Invasive fungal sinusitis | Blitzer 1980 *(104)* | Mortality in 50/126 patients (60%) with DM vs. 38/53 (72%) without DM |
| | Parikh 2004 *(107)* | Mortality in 4/10 patients (40%) with DM vs. 4/35 (11%) without DM |
| Deep neck infections | Chen 2000 *(111)* | Complications in 10/30 patients (33%) with DM vs. 7/75 (9%) without DM ($p = 0.006$) Length of stay 12.7 d with DM vs. 6.7 d without DM ($p = 0.0001$) |
| | Huang 2005 *(112)* | Complication in 19/56 patients (34%) with DM vs. 11/129 (38%) without DM ($p < 0.0001$) Length of stay 19.7 d with DM vs. 10.2 d without DM ($p < 0.0001$) |
| Endocarditis | Bishara 2004 *(121)* | Median Survival 33.13 mo with DM vs. 79.4 mo without DM ($p =$ NS); DM NS on multivariate analysis |
| | Chu 2004 *(120)* | OR 2.48 (2.3–7.7) |
| Influenza | Valdez 1999 *(117)* | OR 4.0 (2.3–7.7) |
| Pneumonia | Fine 1997 *(115)* | OR 1.3 (1.1–1.5) |
| | Valdez 1999 *(117)* | OR 4.0 (2.3–7.7) |
| | Falguera 2005 *(118)* | 18 deaths (17%) with DM vs. 40 deaths (8%) without DM ($p = 0.002$) |
| | Houston 1997 *(116)* | OR 1.66 (0.54–5.07) |
| | McAlister 2005 *(119)* | OR 1.0 (0.69–1.45) |
| Hepatitis | Huo 2003 {HBV} *(123)* | 5 yr survival in HBV-related HCC 73% without DM vs. 41% with DM ($p = 0.015$); in HCV-related HCC 73% without DM vs. 42% with DM ($p = 0.616$) Persistent hepatitis 62% of 39 without DM vs. 39% of 39 with DM ($p = 0.012$) |
| | Huo 2000 *(122)* | OR of cirrhosis 5.2 d (2.0–13.5) |
| UTI | Horcajada 2003 *(136)* | Length of stay 5.2 d for DM vs. 3.9 d without DM ($p = 0.006$) |
| | Leibovici 1991 *(100)* | Mortality in 35/124 patients (28%) with DM vs. 146/504 (29%) without DM ($p =$ NS) |

(*Continued*)

Table 5
(*Continued*)

| | | *Outcomes related to presence of diabetes* |
|---|---|---|
| Necrotizing fasciitis | Pessa 1985 *(150)* | Mortality for DM 5/8 (62.5%), no DM 6/25 (24%) |
| | Gozal 1986 *(151)* | Mortality 2/5 (40%) for DMvs. 0/8 without DM |
| | Korkut 2003 *(154)* | Mortality 9/25 (36%) for DM, 0/20 no DM ($p = 0.002$) |
| | Yeniyol 2004 *(155)* | Mortality 4/18 (22%) for DM, 2/25 (8%) no DM |
| Foot ulcers | Currie 1998 *(158)* | RR death 2.83 (1.93–4.13) |

Outcome refers to mortality unless otherwise stated. Where available, risk ratios are followed by confidence intervals in parentheses. Confidence intervals are 95% confidence intervals except for Shah et al *(96)* which reported 99% confidence intervals. Absolute values are followed by measures of statistical significance ( p-values) in parentheses where available. RR, relative risk; OR, odds ratio; NS, nonsignificant.

Table 6
**Infectious diseases and diseases complicated by infection for which glycemic control may affect outcomes**

| | | *Outcomes related to glycemic control* |
|---|---|---|
| Any infection | Leibovici 1996 *(93)* | OR 3.3 (1.8–6.2) for A1c above the median (10.3%) on logistic regression |
| Pneumonia | Kinzel 1988 *(114)* | Site 1: mortality 6/18 (33%) with hyperglycemia vs. 4/29 (14%) without hyperglycemia ($p < 0.05$) Site 2: mortality 3/10 (30%) with hyperglycemia vs. 5/38 (13%) without hyperglycemia ($p < 0.05$) |
| | McAlister 2005 *(119)* | Mortality in 36/279 patients (13%) with admission glucose $> 11$ mmol/L, vs. 197/2192 (9%) with glucose $< 11$ mmol/L |
| Hepatitis | Kwon 2005 *(128)* | Multivariate analysis for glycemic control: $X^2$ 7.0 ($p = 0.0081$), NS for HBV |
| Necrotizing fasciitis | Nisbet 2002 *(153)* | Poor glycemic control correlated with more extensive debridement ($r = 0.778$)Hospital stay 28.1 d without DM vs. 34 d with DM ($p < 0.01$) |
| Foot ulcers | Apelqvist 1992 *(156)* | A1c 9.0% in patients who healed vs. 8.7% in those requiring amputation ($p =$ NS) |
| | Mantey 1999 *(160)* | A1c 8.5% in those with relapse vs. 7.6% in those without relapse ($p = 0.03$) |
| | Margolis 2000 *(163)* | OR of healing for A1c 1.03 (0.97–1.10) |

Outcome refers to mortality unless otherwise stated. Where available, risk ratios are followed by confidence intervals in parentheses. Confidence intervals are 95% confidence intervals except for Shah et al *(96)* which reported 99% confidence intervals. Absolute values are followed by measures of statistical significance ( *p*-values) in parentheses where available. OR, odds ratio, NS, nonsignificant.

analysis of 105 cases of deep neck infection over from 1987 to 1996, 30 of whom had diabetes *(111)*. Patients with diabetes were more likely to require surgery, develop complications, and have longer hospital stays. An analysis of cases between 1997 and 2002 found similar results *(112)*. Neither author addressed the contribution of glycemic control.

### Pneumonia

In a prospective study of 2471 patients, admission glucose was a significant predictor of adverse outcomes and prolonged length of stay *(119)*. Furthermore, those with an admission glucose $> 200$ mg/dL had an increased risk

of death (13 vs. 9%, $p = 0.03$). For every mmol/L (18 mg/dL) increase in glucose, the risk of death increased 8% (1–15%). This relationship persisted independent of the presence of pre-existing diabetes and therefore may be a marker of physiologic stress rather than a causative factor. This finding was also observed in another study *(114)*. A meta-analysis of 122 articles on community-acquired pneumonia reported a modest increased risk of mortality in patients with diabetes (OR 1.3, 95% CI 1.1–1.5) *(115)*. However, only 5 studies reported data on diabetes. In addition, Thomsen et al found that pneumococcal bacteremia was more common in patients with diabetes but there was no increase in mortality *(102,103)*. Except in the ICU, it is unclear whether glycemic control will improve outcomes.

### Urinary Tract Infections

Much of the data regarding urinary tract infection in patients with diabetes is in women. A prospective controlled study of 799 postmenopausal women without diabetes and 218 women with diabetes found a higher risk of UTI among patients with diabetes (relative risk of 1.8, 95%CI 1.2–2.7) *(138)*. There was no clear relationship to HbA1c in this study or other studies *(132–134)*, but there was an association with need for any pharmacologic therapy *(134)*, insulin *(138)*, and diabetes duration *(132,138)*. A prospective case-control study of 54 patients with community-acquired febrile UTI found that patients with diabetes were more likely to require a prolonged hospital stay (5.2 vs. 3.9 d, $p = 0.006$) *(136)*.

Scholes et al reported that patients with diabetes were more likely to be hospitalized with pyelonephritis, but this did not translate to higher mortality *(139)*. This may be owing to a higher incidence of occult upper urinary tract infection *(132)*. On the other hand, emphysematous pyelonephritis, a rare complication occurring most commonly in patients with diabetes, carries a high mortality (40% in1 series) *(141,142)*. Papillary necrosis is another severe complicated form of urinary tract infection seen with increased frequency in diabetes *(140)*. A mean A1C of 9.7 ± 3.7% was reported among patients having papillary necrosis and type 2 diabetes. There is also an increased risk for fungal urinary tract infection, emphysematous cystitis, and perinephric abscess.

### Soft Tissue Infections

Patients with diabetes are at increased risk for developing soft tissue infections *(98)*. Among patients with necrotizing soft tissue infections, the length of hospitalization is predicted by hyperglycemia *(152)*.

### Fournier's Gangrene

In a case series of 26 patients with Fournier's gangrene, the presence of poor glucose control correlated with need for extensive debridement ($r = 0.778$) and patients with diabetes had longer hospital stays (28.1 vs. 34 d, $p < 0.01$) *(153)*. This did not translate to increased mortality. Diabetes did not affect outcomes in another study *(155)*, but the largest series of 45 patients found that diabetes was an independent predictor of mortality *(154)*.

### Lower Extremity Infections

Lower extremity infections are common in patients with diabetes, particularly in the presence of neuropathy and peripheral vascular disease. An observational study demonstrated that the risk of admission for peripheral vascular disease, neuropathy, and ulceration was 7 times greater for patients with diabetes than those without *(158)*. The average length of stay for patients with diabetes was twice that for those without diabetes, and inpatient mortality (RR 2.83, 95%CI 1.93–4.13) and amputation rates (RR 34.52, 95% CI 26.27–45.37) were higher in patients with diabetes. Patients with diabetes accounted for 87% excess in costs.

Hyperglycemia is not one of the classic triad of factors (ischemia, neuropathy, trauma) predisposing to the initial development of lower extremity foot ulcers. It appears that short-term glycemic control does not affect the occurrence or outcome of lower extremity infections *(156)*. The A1C and treatment modality for hyperglycemia have not been shown to predict the outcome of conservative management of foot infections, once these ulcers are established *(156,159,161,163)*. On the other hand, properly powered studies of intervention with stringent control are not available. HbA1c was associated with ulcer relapse in1 study (8.5 ± 1.7% vs. 7.6 ± 1.2% in patients with or without recurrence respectively, $p = 0.03$) *(160)*. Relapse was not associated with duration or type of diabetes, or type of therapy. The development of infection leads to impaired wound healing, hospitalization, and

amputations and, when owing to *Staphylococcus aureus*, the development of infection is associated with increased mortality *(156,162,164,165)*.

It is unknown whether tight glycemic control will promote healing. A feasibility study examining this question was abandoned at 20 wk owing to insufficient recruitment *(173)*. In the UKPDS, there was a nonsignificant (36%) reduction in amputations in the intensively managed group *(3)*.

### HIV

Shah et al reported a similar prevalence of diabetes in patients with or without HIV. Therefore, it appears that antiretroviral therapy accounts for most cases of diabetes associated with HIV (see section on medication-induced hyperglycemia). In a retrospective chart review *(174)*, only 27 (1.9%) of 1,392 patients met the case definition for hyperglycemia (glucose greater than 250 mg/dL on two separate occasions). Twelve *(12)* of these were pre-existing, and 12 of the remaining 13 cases were drug-associated.

## *Other Illnesses*

### Chronic Obstructive Lung Disease

Because hyperglycemia in the hospital among patients admitted with exacerbations of chronic obstructive lung disease is associated with worse outcomes *(175)*, it is reasonable to suppose that preadmission glycemic control has a bearing on subsequent outcomes.

### Cardiovascular Illness

Hyperglycemia is associated with worse outcomes postmyocardial infarction and after coronary artery bypass *(32,43,48,176–180)*. Furthermore, there is evidence that outcomes are improved with tight glycemic control *(30–33,35)*.

Patients with diabetes are much more likely to develop heart failure than those without diabetes. In a recent health maintenance study of over 8,000 patients with diabetes and similar number of controls, the incidence of CHF was 30.9 versus 12.4 cases per 1,000 person-years (rate ratio 2.5, 95% CI 2.3–2.7) *(181)*. HbA1c was associated with increased risk (HR 1.32 per percentage point). Patients who developed heart failure were more likely to be using insulin and have longer diabetes duration. In another study, each 1% increase in HbA1c was associated with 12% increased risk of heart failure (95% CI 8–16%) *(182)*. In the DIGAMI study, glycemic improvement using long-term subcutaneous insulin improved 1-yr mortality, of which CHF accounted for 66% of deaths overall. CHF accounted for 72% of deaths in insulin-treated and 62% of control patients *(30)*. This did not reach statistical significance, and the number of deaths overall was small.

### Gastroenterologic Illness

Diabetes may cause chronic gastrointestinal symptoms directly via hyperglycemia-mediated gastric slowing, or via autonomic neuropathy. In two population-based surveys, Bytzer et al found that patients with diabetes reported significantly more gastrointestinal symptoms than controls *(183,184)*. The presence of symptoms was associated with the quality of self-reported glycemic control *(183,184)* or HbA1c *(184)*. Symptoms were not related to type of therapy for hyperglycemia. In addition, attainment of euglycemia may improve symptoms. In a controlled trial, Sogabe et al reported that baseline gastric emptying was significantly delayed among 30 patients with upper abdominal symptoms who were hospitalized with poor glycemic control. After 1 mo, a reduction in HbA1c from 10.1 ± 1.90% to 8.69 ± 1.45% was associated with normalization of gastric emptying and improvement in symptom scores. Conversely, it might be possible that normalization of gastric emptying might also improve glycemic control through more predictable mealtime glucose influx. Unfortunately, a study that examined this possibility using Cisapride failed to demonstrate either an improvement in hyperglycemia or gastric emptying *(185)*.

### Cirrhosis

Patients with type 2 diabetes have an increased risk for hepatic failure and there is evidence that patients with chronic liver disease are at increased risk for diabetes. In1 series, diabetes was present in 28% of the 361

subjects with variable causes of cirrhosis *(186)*. The diagnosis of diabetes preceded the diagnosis of cirrhosis in 44 patients, followed the diagnosis of cirrhosis in 25 patients, and occurred simultaneously in 31 patients. Diabetes was an independent risk factor for long-term (5 yr) mortality, mainly owing to hepatocellular failure. It is unclear whether diabetes is simply a marker of hepatic failure and the glucose dysregulation that ensues *(187)* or whether it may be causative of hepatic failure. Studies do show that diabetes is more common in patients with hepatitis C (HCV) than hepatitis B (HBV) (43.3% vs. 19.7% respectively, $p = 0.00001$) *(128)*. This was confirmed in another study and indicates that the risk of diabetes may be specific to the cause *(127)*. However, this risk is also dependent on the severity of hepatic failure *(124,127,129)* and pre-existing diabetes risk factors *(126)*. Not all studies have shown an increased risk of diabetes in patients with HCV *(125)*. Finally, Kwon et al found that glycemic control was an independent predictor of mortality for HCV *(128)*. It is unknown whether tight glycemic control improves outcomes.

### Pancreatitis and Hypertriglyceridemia

It has been suggested that insulin therapy, activating lipoprotein lipase, may confer specific benefit in the treatment of hypertriglyceridemia and pancreatitis *(188–192)*.

### Renal Disease

Patients with diabetes are at increased risk for end-stage renal disease. Two retrospective analyses of patients on continuous ambulatory peritoneal dialysis identified predialysis glycemic control as an independent predictor of mortality *(193,194)*. Glucose levels did not affect the distribution of cause of death *(193)* and mode of therapy had no effect *(194)*. Once end stage renal disease has developed, it is unknown whether interventions to improve glycemia may improve outcomes.

### Musculoskeletal Disorders

Much of the aberrations of glucose control in reference to musculoskeletal disorders occur in patients treated with glucocorticoids.

### Malignancy

Epidemiological studies suggest an increase in risk of diabetes in several types of cancers as shown in Table 7 *(195–214)*. Furthermore, there may be a link between glycemic control and outcomes, but it is not known whether intervention will improve outcomes *(215)*. For example, Weiser et al discovered that acute lymphocytic leukemia patients with hyperglycemia (defined as two or more glucose determinations of $>200$ mg/dL during induction chemotherapy) had shorter mean complete remission duration (24 vs. 52 mo, $p = 0.001$), shorter median survival (29 vs. 88 mo, $p < 0.001$) and had increased risk of infection and sepsis *(64)*. In a prospective study of patients with colon cancer, those with diabetes had a 42% increased risk of death from any cause ($p < 0.0001$) and 21% increased risk for recurrence ($p = 0.05$) compared to those without diabetes *(216)*. This increased risk was reported in other studies *(197,199)*. Furthermore, Saydah et al reported patients in the highest quartile of HbA1c had an odds ratio of 1.57 (95% CI 0.94–2.60, $p = 0.02$) for the development of colon cancer *(217)*. A fascinating area for future investigation is the possible relationship between treatment modality used for diabetes and cancer risk *(218)*.

### Endocrine Disease

Several endocrine disorders are associated with aberrations of glucose regulation, which may improve after treatment of the underlying condition, as shown in Table 8 *(219–230)*. For example, in Cushing's disease, the degree of hyperglycemia is correlated with cortisol levels *(221)*. However, even 5 yr after cure, abnormalities of glucose may persist *(220)*. Hyperthyroidism may exacerbate diabetes and may also precipitate diabetic ketoacidosis *(230)*. In an observational analysis of 70 patients *(229)*, diabetes preceded the onset of hyperthyroidism in 63 patients, and was simultaneous in 7 patients. 51% of patients had worsening of glycemic control, whereas 21% had improvements after achieving euglycemia.

Table 7
Malignancies and the role of diabetes or hyperglycemia

| | |
|---|---|
| | *Risk is associated with hyperglycemia or diabetes* |
| Gastric cancer | |
| Davey-Smith 1992 *(195)* | RR 2.29 (0.72–7.25) |
| Jee 2005 *(196)* | HR 1.16 (1.04–1.28) |
| Yamagata 2005 *(296)* | IR 4.5 (2.8–6.2) for FBG $>5.8$ mmol/L vs. FBG $<5.3$ mmol/L |
| Colon cancer | |
| Davey-Smith 1992 *(195)* | RR 0.62 (0.09–4.47) |
| Hu 1999 *(197)*: | RR 1.43 (1.10–1.87) |
| Saydah 2003 *(198)* | OR for A1c $>5.78$ was 1.57 (0.94–2.60, $p=0.02$) |
| Limburg 2005 *(199)* | RR 1.4 (1.1–1.8) |
| Jee 2005 *(196)* | HR 1.28 (1.06–1.55) |
| Pancreatic cancer | |
| Davey-Smith 1992 *(195)* | RR 5.27 (1.90–14.60) |
| Gullo 1994 *(200)* | OR 3.04 (2.21–4.17) for all patients with DM;<br>OR was 1.43 (0.98–2.07) for patients with DM $>3$ yr |
| Jee 2005 *(196)* | HR 1.71 (1.42–2.06) |
| Gapstur 2000 *(201)* | RR 2.15 (1.22–3.80) |
| Huxley 2005 *(202)* | RR 1.82 (1.66–1.89) |
| Stolzenberg-Solomon 2005 *(203)* | HR 2.13 (1.04–4.35) |
| Endometrial cancer | |
| Anderson 2001 *(204)* | RR 1.43 (0.98–2.1) |
| Furberg 2003 *(206)* | RR 2.41 (1.08–5.37) |
| Bladder cancer | |
| Davey-Smith 1992 *(195)* | RR 1.13 (0.84–1.52) |
| Tripathi 2002 *(207)* | RR 2.46 (1.32–4.59) |
| Jee 2005 *(196)* | HR 1.45 (0.96–2.19) |
| Breast cancer | |
| Michels 2003 *(208)* | HR 1.17 (1.01–1.35) |
| Esophagus | |
| Davey-Smith 1992 *(195)* | RR 4.32 (1.03–18.07) |
| Jee 2005 *(196)* | HR 1.36 (1.08–1.71) |
| Hepatocellular Carcinoma | |
| Jee 2005 *(196)* | HR 1.59 (1.45–1.74) |
| Prostate | |
| Bonovas 2004[a] *(209)* | RR 0.91 (0.86–0.96) |
| Chan 2005 *(210)* | OR 0.95 (0.95–1.02) |
| Coker 2004[a] *(211)* | adjusted OR 0.64 (0.45–0.91) |
| Gonzalez-Perez 2005[a] *(212)* | OR 0.72 (0.59-0.87);<br>Treated DM OR 0.63 (0.50-0.80);<br>Untreated DM OR 1.01 (0.73–1.40) |
| Rodriguez 2005[a] *(213)* | RR 0.67 99 (0.60–0.75) |
| Tavani 2002 *(214)* | OR 1.02 (0.75–1.40) |
| Jee 2005 *(196)* | HR 1.13 (0.75–1.70) |
| Davey-Smith 1992 *(195)* | RR 1.02 (0.84–1.26) |
| Hematologic malignancy | |
| Jee 2005 *(196)* | HR 1.53 (1.08–2.15) |
| Davey-Smith 1992 *(195)* | RR 0.90 (0.74–1.10) |

(*Continued*)

**Table 7**
**(*Continued*)**

| *Outcomes are associated with hyperglycemia or diabetes* | |
|---|---|
| Small cell carcinoma<br>Maestu 1997* *(215)* | Hyperglycemia was a significant predictor of deathon univariate analysis but not multivariate analysis |
| Acute lymphocytic leukemia<br>Weiser 2004 *(64)* | Hyperglycemia was associated with shorter completeremission duration (24 vs. 52 mo ($p < 0.001$), shorter median survival 29 vs. 88 mo ($p < 0.001$) |
| Colon canrcinoma<br>Meyerhardt 2003* *(216)* | Disease-free survival 48% DM, 59% without DM ($p < 0.0001$); overall survival 57% DM vs. 66% survival without DM ($p < 0.0001$) |

Where available, risk ratios are followed by 95% confidence intervals in parentheses. Absolute values are followed by measures of statistical significance ($p$-values) in parentheses where available. RR, relative risk; HR, hazard ratio; OR, odds ratio, NS, nonsignificant.
[a]Studies for which diabetes is associated with lower risk of the given malignancy.

**Table 8**
**Endocrine disorders which may affect diabetes management**

| | *Increased risk of DM or worsening of glycemic control* | *Predictor of mortality* | *Normalization of hormone results in improvement of glycemia* |
|---|---|---|---|
| Cushing's syndrome | | | |
| Extabe 1994 *(219)* | DM: 19/49 (39%), IGT: 12/49 (24%), NGT: 18/49 (37%) | Glucose independent predictor of death ($p < 0.01$) | 53% reduction in DM after cure |
| Colao 1999 *(220)* | | | 5 yr after cure, FBG and OGTT value significantly greater in patients than controls |
| Mancini 2004 *(221)* | DM: 23/49 (47%), IGT: 11/49 (22%), NGT: 15/49 (31%) | | |
| Pheochromocytoma | | | |
| La Batide-Alanore 2003 *(223)* | OR for DM 5.5 (3.5–8.7) | | DM resolved in 89.5% (51/57) |
| Wiesner 2003 *(224)* | | | GIR decreased in patients with/without DM ($p < 0.05$), DM resolved in 3/5 patients |
| Stenstrom 1984 *(222)* | FBG $> 126$ mg/dL present in 24% of patients not previously suspected of DM | | DM resolved in 28/29 patients (96.6%) without previous diagnosis |
| Acromegaly | | | |
| Holdaway 1999 *(225)* | DM 18 vs. 2.8% of control | | DM decreased by 61% if cured, 6% if not cured |
| Kasayama 2000 *(226)* | HOMA-IS lower in patients with AM than controls ($p < 0.0001$); DM or IGT in 12/24 patients(50%) | | HOMA-IS increased to normal after cure; 2/7 with IGT/DM pre-op normalized after cure |
| Holdaway 2004 *(225,227)* | | DM incidence 22% in survivors vs. 61% in nonsurvivors ($p < 0.01$) | |

(*Continued*)

Table 8
(*Continued*)

| | *Increased risk of DM or worsening of glycemic control* | *Predictor of mortality* | *Normalization of hormone results in improvement of glycemia* |
|---|---|---|---|
| Serri 2004 *(228)* | | | IGT/DM 7/34 (21%) with remission vs. 11/19 (58%) with persistant AM ($p = 0.006$); OR for IGT/DM with elevated IGF-1 13.6 (2.5–73.7, $p = 0.008$) |
| Hyperthyroidism | | | |
| Cooppan 1980 *(229)* | Deterioration of glycemic control occurred in 32/70 patients with DM; increased insulin by mean of 50% in 11/48 patients | | Insulin decreased in 13/48 patients (27%) by mean 35%; 4/22 patients (18%) on oral agents progressed to insulin |
| Sola 2002 *(230)* | 3 cases of DKA precipitated by hyperthyroidism | | |

Where available, risk ratios are followed by 95% confidence intervals in parentheses. Absolute values are followed by measures of statistical significance ( *p*-values) in parentheses where available. IGT, impaired glucose tolerance; NGT, normal glucose tolerance; FBG, fasting blood glucose; OGTT, oral glucose tolerance test; OR, odds ratio; GIR, glucose infusion rate; HOMA-IS, homeostasis model assessment of insulin sensitivity; AM, acromegaly.

### Central Nervous System Disease

Hyperglycemia is associated with worse outcomes in stroke, including mortality and infarct expansion *(45,46, 231,232)*.

### Psychiatric Disease

There is considerable evidence to support a link between depression and diabetes. This is discussed in detail elsewhere in this book. In addition, atypical antipsychotic medications are associated with exacerbation of glycemic control or development of overt diabetes (see section on medications affecting glycemic control).

## TREATMENT OF TYPE 2 DIABETES DURING CONCOMITANT ILLNESS

### *General Strategies during Illness*

Testing of blood glucose at least 4 times daily is important for detection of hyperglycemia. If blood glucose is severely elevated over 240 mg/dL for 3 or 4 successive tests or for 24 h, patients should be evaluated for possible dehydration, especially the elderly. Illness or fever without improvement over several days should be evaluated.

Depending upon appetite and presence of nausea, meals may have to be modified to a clear liquid or soft diet. Otherwise, it is desirable to recommend a consistent carbohydrate diet containing 4 servings of carbohydrate at meals and 1–2 servings at snacks, such that the caloric needs of the patient are met by a diet that he or she can tolerate. Fluid intake should be encouraged *(233)*. The website of the American Diabetes Association maintains patient recommendations stated in lay terms.

## *Common Low-Risk Illnesses*

### Viral Respiratory Infection

Upper respiratory infections without fever or purulence frequently are so short-lived and uncomplicated that conversion to insulin seldom is required. Sugar-free cough syrups and avoidance of sympathomimetic-containing nasal decongestants commonly are recommended. For those already taking insulin, correction doses of short-acting or rapid acting insulin are given for hyperglycemia.

### Gastroenteritis

In most cases of acute gastroenteritis the state of hydration and electrolyte status present greater dangers to the patient than the underlying illness. Patients should be encouraged to drink fluids throughout the day, sipping a little at a time, and may use bouillon, electrolyte-containing beverages, and clear liquids containing glucose while acutely ill. Metformin, GLP-1 analogs and alpha-glucosidase inhibitors should be discontinued. Unless carbohydrate exposure is possible and hypoglycemia is absent, insulin secretogogues often have to be interrupted. On the other hand, some patients are able to ingest carbohydrates. Some become hyperglycemic. Persistent hyperglycemia above 240 mg/dL, failure to retain fluids, inability to produce urine, or symptoms of dehydration such as orthostatic dizziness, severe weakness, or lethargy should prompt medical evaluation. Persistent vomiting or diarrhea for over 6 h should be evaluated.

## *Tolerability, Safety, Effectiveness and use of Antihyperglycemic Agents*

In the presence of an intercurrent or concomitant illness, in the ambulatory setting the principal dilemmas confronting a clinician are whether to instruct a noninsulin using patient on the use of insulin (whether to plan a "new insulin start") and whether to interrupt other antihyperglycemic therapy.

Multiple drugs eventually are required for maintenance of control even among patients who have no intercurrent illness *(234–238)*. The drug most consistently capable of achieving normoglycemia is insulin *(239)*. As insulin is started, the possibility of edema presents an argument in favor of dose reduction or interruption of maximum dose thiazolidinediones. An argument in favor of interruption of sulfonylureas is the possibility of excessive prandial effect, once prandial insulin is started. Arguments against interruption of these drugs are the risks of temporary destabilization of blood glucose during insulin dose titration.

The safety of metformin has been demonstrated when prescribing guidelines are observed. The risk of continuation is the small risk of lactic acidosis. Interruption of metformin is recommended if any of the following conditions exist: renal failure, hypoxia, acute or chronic metabolic acidosis, congestive heart failure requiring pharmacologic therapy, cardiovascular collapse, septicemia, myocardial infarction, contrast administration, or hypersensitivity to the drug. Caution should be observed in the presence of major surgical procedures, impaired liver function, suspected alcohol abuse, and advanced age.

Evidence-based guidelines on interruption of pramlintide and exenatide during intercurrent illness have not been developed *(240–244)*. One of the principal concerns would be the risk of exacerbation of nausea, emesis, fluid and electrolyte disturbance, and possibly hypotension with its consequences. These drugs are contraindicated in the presence of gastroparesis. However, the treatment guideline on gastroparesis does not differentiate among temporary reversible gastroparesis owing to electrolyte disturbance, other drug therapy, or intercurrent illness and gastroparesis owing to autonomic neuropathy. The use of exenatide is not recommended for creatinine clearance $< 30$ cc/hr. Interruption of exenatide or pramlintide would not be expected to destabilize the glycemic control markedly in the short run, nor would continuation or dose augmentation be expected to adequately address the increased basal insulin requirement that commonly accompanies intercurrent illness *(245)*. Therefore, the authors favor temporary interruption of these drugs during intercurrent illness.

To avoid nausea upon reintroduction of exenatide or pramlintide after prolonged interruption of these drugs, dose retitration may be necessary from an initial low restarting dose. The question may arise whether exenatide or pramlintide was the sole cause of an episode of emesis. The question also may arise whether patient selection for exenatide or pramlintide therapy had been well advised before the development of the illness, given comorbidities and the risk to the patient that might arise from clinical episodes of emesis or dehydration. Drug reintroduction at a lower starting level can be considered based on clinical evaluation.

For insulin users experiencing hyperglycemia, the scheduled doses of insulin may have to be increased until other drugs that had been interrupted can be reinstituted. For short-term intercurrent illnesses, it is safest to avoid making large adjustments to intermediate or long acting components of insulin therapy. Patients may be instructed on the use of correction doses of short acting insulin or rapid acting analog, which can be administered as often as 5 times daily according to an algorithm that might be easy to implement, perhaps having only 2 levels, starting at +1 or +2 units of rapid acting analog for blood glucose 150–199 and +2 or +4 units for blood glucose 200 or higher, with individualization and possible use of higher amounts according to patient sensitivity or resistance. If the patient is severely hyperglycemic, correction doses can be used at bedtime and during midsleep, sometimes at a lower dose than prandially. The risk for hypoglycemia must be weighed against the need for correction dose therapy.

For insulin users, if blood glucose monitoring yields results below 100 mg/dL, those patients using only basal insulin or premixed insulin should consider making at 50% dose reduction. Patients using basal-prandial-correction therapy should withhold prandial doses until 50% of their meal is taken, and should consider making reductions of basal insulin as described below under "preparation for procedures."

### *The Prepared Practice*

For some patients, a decision might be made that glycemic control is important enough to outcome, or the presence of diabetes confers a serious enough risk factor, that hospitalization is necessary for the purpose of gaining glycemic control and/or caring for the underlying condition. Strictly medical considerations include but are not limited to the expected duration of illness, prognosis of the underlying condition with and without glycemic control, the possibility that there is a critical window of time during which glycemic control is important to outcome, disease-specific or patient risk factors for dehydration or hyperglycemic emergency, and the realistic possibility of safely reaching target blood glucose within a useful timeframe via the subcutaneous route of insulin use.

For many hyperglycemic patients, if patient factors and office logistics were not at issue, the outpatient dilemma undoubtedly would be decided most of the time in favor of a same-day outpatient "new insulin start." The decision that might be rendered for a given case scenario, unfortunately, is likely to differ depending on whether or not the patient has had prior history of insulin and has retained knowledge of previous instruction on insulin use *(246,247)*. For those patients not knowledgeable in the use of insulin, variables include patient knowledge of options for contact with healthcare professionals in relation to office hours, knowledge of self-monitoring, acceptance of insulin therapy, readiness to learn the use of insulin in the face of illness, comprehension of a possibly rapid dose titration program, socioeconomic factors, and the home support system *(87,88,248)*. There are additional factors over which a practice group has substantial control, such as telephone support and telephone access offered by the practice, the methods of off-hours contact by which intercurrent illness is reported, the open access orientation or lack thereof on the part of the practice group, and proficiency and availability of office staff to serve possible educational needs acutely. Active strategies are required to combat therapeutic inertia in general *(249,250)*, but in particular the need exists for advance planning to be able to implement insulin therapy for acute illness, when insulin is thought to be medically desirable. We believe that active strategies to facilitate availability of urgent care, including education on new insulin starts for acute illness, should be developed by any practice group attempting to serve as front-line medical contact for patients having diabetes *(251–256)*.

For residents in a chronic care facility having supervision of medical care, conversion to insulin is especially easy to implement.

#### The Decision to Convert to Insulin

An argument in favor of intensive outpatient management could be based on observational data showing a relationship between outcomes and glycemic control upon arrival at the hospital *(44)*. If the patient is hospitalized with a critical illness, glycemic control reduces morbidities and mortality. Some of the risk reduction relates to conditions that are treated only in the hospital or intensive care unit (ventilator dependency, acute renal failure, transfusion requirement, arrhythmia or pump failure in relation to myocardial infarction and heart surgery); however, sepsis and sepsis-related mortality are also reduced by intensive glycemic control in the hospital *(22,29,36,38,39,47)*. The concept of a critical window of time has been demonstrated most clearly in relation to

postoperative complications *(33,40,61–64,257)*. For most open wounds and invasive bacterial or fungal infectious processes, the time to target probably should be a matter of hours. For given disease entities that could require hospitalization, especially those that could be considered surgical problems (open wounds), or those that could eventuate in critical illness (such as lower respiratory tract infection or urinary tract infection with fever), distinction between inpatient and outpatient status is somewhat artificial; the underlying pathophysiology of complications does not change upon crossing the threshold of the hospital. Therefore, for community acquired infections that might evolve to require hospitalization, we argue that glycemic control might confer an advantage in the preadmission phase.

Sometimes for a given condition insulin might have specific advantages, aside from its potency, in comparison to the use of alternative hypoglycemic agents. These conditions include chronic renal failure, where safety issues limit the use of oral agents *(258,259)*; severe hypertriglyceridemia with or without pancreatitis, where insulin has specific beneficial action upon lipoprotein lipase; and other conditions which, if they were to destabilize, would create risk for lactic acidosis, such as chronic relapsing pancreatitis.

Concomitant patient factors (other than new major medical illnesses) sometimes create recognizable risk for hyperglycemic hyperosmolar state, such that education in the use of insulin is prudent. Known risk factors include peritoneal dialysis, thiazide diuretic therapy, and corticosteroid therapy *(75–78,80,82,83,260,261)*.

At the early stages of an intercurrent illness, it is necessary to consider whether a person having diabetes is at particular risk for a complicated course, including progression from asymptomatic to symptomatic disease *(133)*, locally invasive or necrotizing infection *(152)*, development of morbid complications of infection, septicemia or systemic inflammatory response syndrome, or fatality *(94,96)*. Some common bacterial infections often result in hospitalization, such as pneumonia, acute cholecystitis, or pyelonephritis. Additional infections that are seen principally among patients having diabetes, such as rhinocerebral mucormycosis, malignant otitis externa, emphysematous cholecystitis, or complicated pyelonephritis (papillary necrosis *(140)*, pyelonephritis *(141)*) routinely require admission. Because severe infections such as these are treated in the hospital, where conversion to insulin should be a matter of routine *(262)*, these advanced infections are not the subject of the present chapter on ambulatory management. However, if an underlying infection is one for which a future decision to hospitalize might depend in part upon glycemic control, outpatient use of insulin is advisable.

A determinant of whether to start insulin might be the question of whether the patient meets target range blood glucose control necessary for recovery from or management of a specific intercurrent condition. With recognition that there is no glycemic threshold above normal for microvascular disease, the established targets for glycemic control in the ambulatory setting are based on risk for microvascular disease *(8,263,264)*. Although the area is controversial, it has been further suggested that not only overall control, but also glycemic variability, is a determinant of risk for microvascular disease, and that postprandial control is a risk factor for macrovascular disease *(265–268)*. In the hospital setting, even though some in vitro data may suggest the blood glucose threshold for neutrophil dysfunction may be as high as 180 mg/dL, it was a lower target of 110 mg/dL using whole blood criteria that achieved the reduction of mortality in the surgical ICU in Leuven, Belgium *(29)*. Although the glycemic target for ambulatory patients might be modified based on risk for hypoglycemia, we do not know of any conclusive evidence that the glycemic threshold for prevention of complications during ambulatory management should be modified based on the specific comorbidity under consideration. As during normal health, the targets for glycemic control for blood glucose are: 70–130 premeal, and under 180 mg/dL peak postprandial *(11)*.

### Specific Conditions Justifying a "New Insulin Start"

It is against the backdrop of use of oral agents in the ambulatory setting that patients having diabetes often develop hyperglycemia in conjunction with another intercurrent condition. If hyperglycemia is present, the authors argue in favor of a "new insulin start" in the ambulatory management of at least the categories of intercurrent illness or situation that are shown in Table 9. Patients commonly welcome aggressive therapy under many of these conditions.

In Table 9, the category of "invasive or potentially invasive infection" includes common conditions such as periapical dental abscess, acute purulent bronchitis, urinary tract infection, infections associated with foreign

Table 9
Conditions justifying a "new insulin start" for control of hyperglycemia among patients whose glycemic control is not at target

- Invasive or potentially invasive bacterial or fungal infection
- Concomitant condition predisposing to development of bacterial or fungal infection
- Individual patient history of previous infection in association with predisposing condition
- Chronic relapsing pancreatitis
- Severe hypertriglycemidemia
- New onset renal failure
- Other organ dysfunction creating risk for renal failure
- Ambulatory preparation for surgery
- Perioperative and postoperative status
- Open or unhealed wound
- Corticosteroid therapy
- Patient risk factors for hyperglycemic hyperosmolar state
- Underlying condition for which decision to hospitalize might depend upon glycemic control

bodies or appliances, and soft tissue infections, as well as other bacterial and fungal infections listed in Tables 3 and 4. The category of "concomitant condition predisposing to bacterial or fungal infection" includes but is not limited to such entities as influenza, exacerbation of chronic obstructive lung disease, obstruction of urine flow, lower extremity ulcer, deep or persistent open wounds, and incompletely healed wounds from recent surgery. The category of "condition predisposing to bacterial or fungal infection" includes any other condition in which there is compromise to host defenses, involving loss of integrity of the skin, impairment of the immune system, or interference with mechanical requirements for defense against infection. Prior episodes of infection in connection with a predisposing condition indicate patient risk for recurrence. We believe preoperative normalization of blood glucose justifies new insulin starts in the ambulatory setting.

### Introducing and Titrating Insulin during Concomitant Illness

In planning a new insulin start, the practitioner must decide upon a starting dose, the components of therapy, and a titration plan. As is true of sliding scale therapy in the hospital, target range control cannot be achieved in the outpatient setting with sliding scale therapy alone *(269)*. A reasonable low estimate of total daily dose of insulin to cover prandial as well as basal insulin requirements is 0.3 units per kilogram. Some programs for gradual titration over many weeks start with bedtime or supper insulin or morning peakless insulin, and continuation of daytime oral agents. A number of forced titration programs have been outlined, with consideration for the ability of the patient to comprehend complexity and the ability of the medical team to support patient ability to implement stepwise dose adjustments. These include forced titration of basal insulin, unmixed or premixed insulin given twice daily or 3 times daily, or basal-prandial-correction therapy *(270–291)*. Diabetes educators, nurse case managers, and Pharm Ds provide invaluable roles in implementing dose titration protocols. A strategy preferred by the authors is shown in Fig. 1, in which basal-prandial-correction therapy is implemented from the outset. The caregiver recommends self-monitoring of blood glucose, informs the patient of the target range for glycemic control, and assigns dates on which daily doses of insulin should be increased in the event that hyperglycemia persists *(285)*.

## *Preparation for Procedures, for Same Day Surgery and For Admission*

Although strong supporting evidence is lacking, the following practices are recommended by the authors for type 2 diabetes patients before procedures that require NPO status.

| Change date (when new doses start) | Units of premeal rapid-acting analog<br>☐ Lispro<br>☐ Aspart<br>☐ Glulisine | Units of glargine or detemir<br><br>☐ Before breakfast<br>☐ Before bedtime |
|---|---|---|
| | 2 | 6 |
| | 3 | 6 |
| | 3 | 9 |
| | 4 | 9 |
| | 4 | 12 |
| | etc. | etc. |
| | 8 | 24 |
| | 10 | 24 |
| | 10 | 30 |
| | 12 | 30 |
| | 12 | 36 |
| | etc. | etc. |
| | 26 | 78 |
| | 28 | 78 |
| | 28 | 84 |
| | 30 | 84 |
| | 30 | 90 |

**Fig. 1.** The caregiver determines starting doses depending upon whether or not insulin previously has been used. A table created in which incremental dose adjustments of 1–2 units of prandial rapid acting analog are shown, alternating with increments of 3–6 units of basal insulin. The caregiver enters change dates. The change dates might occur every 1–3 depending upon urgency. A correction dose algorithm can be included, such as +1 or +2 units of rapid acting analog for blood glucose 150–199 mg/dL and +2 or +4 units of rapid acting analog for blood glucose over 200 mg/dL, or higher amounts depending upon insulin resistance (figure modified from Reference 274).

If the patient takes long-acting insulin analog, the dose of long-acting analog for type 2 diabetes should be reduced to 25% of the total daily insulin dose on the night preoperatively or before a procedure requiring NPO status. If the patient has been troubled with hypoglycemia during daily living, an additional 20% reduction of the planned preoperative basal insulin dose should be made before the procedure. (The total daily insulin dose is computed as the total amount of insulin of any kind taken per 24-hr).

Patients with type 2 diabetes who normally use premixed insulin twice daily generally can safely take the insulin on the night before their procedure but should withhold the morning dose until after the procedure. Additional vigilance for hyperglycemia is required on the day of the procedure. Blood glucose should be checked before the procedure, and supplemental subcutaneous insulin should be given before the procedure or an intravenous insulin infusion should be initiated, depending upon the nature of the procedure and the protocols of the facility at which the procedure will be performed.

Patients who normally take oral agents should withhold their morning dose on the day of a procedure. The physicians receiving the patient should test blood glucose upon arrival. Readings over 140 to 180 mg/dL might justify correction therapy with subcutaneous insulin before the procedure, depending upon the nature of the procedure. In the case of major surgery, an intravenous insulin infusion can be started upon arrival.

### *Postdischarge Care*

Owing to anorexia and altered organ function, the postdischarge time following hospitalization is a period of especial vulnerability to hypoglycemia, especially for the elderly and for patients on certain drugs such as insulin or glyburide *(259)*.

For patients who were poorly controlled before admission or who had been experiencing hypoglycemia alternating with hyperglycemia, the hospitalization often provides a "teachable moment" to introduce the idea of intensification after discharge. Some patients who wish to use basal-prandial correction insulin therapy will need several hours with a diabetes educator to learn the skills of advanced carbohydrate counting, and others will benefit from reinforcement of basic skills *(292–294)*. At the time of discharge, parameters should be provided for reassessment before the intended reappointment, but otherwise there should be follow-up with the primary care provider within 2 wk.

## SUMMARY

For patients having type 2 diabetes, low-risk intercurrent illnesses often are managed conservatively in the ambulatory setting. During higher risk intercurrent illnesses or conditions, conversion to intensive insulin therapy is justified when glycemic targets are not met on regimens that do not include insulin. These conditions include invasive or potentially invasive bacterial or fungal infection, the presence of a concomitant condition predisposing to development of bacterial or fungal infection, individual patient history of previous infection in association with a predisposing condition, and ambulatory preparation for surgery. The design of a practice must accommodate potential patient need for rapid conversion to insulin therapy. Hospitalization is an ideal opportunity for intensification of previously unsatisfactory treatment regimens. Outpatient follow-up should include meetings with a diabetes educator and the primary care provider.

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# 15 Adherence to Practice Guidelines for People with Diabetes Mellitus

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***CONTENTS***



**Key Words:** Adherence; diabetes; guidelines; insulin; dyslipidemia; hypertension.

## INTRODUCTION

The incidence and prevalence of diabetes have increased to epidemic proportions. Practice guidelines largely supported by randomized controlled clinical trials provide therapeutic targets that, if met, would dramatically reduce the morbidity and mortality associated with diabetes. Yet adherence by both patients and their health care professionals to these guidelines and to specific therapeutic recommendations designed to achieve guideline targets remains much less than optimal. This chapter will discuss the level of adherence to guidelines and speculate on both causes and potential remedies for suboptimal adherence.

## PREVALENCE AND COST OF DIABETES

The Centers for Disease Control and Prevention (CDC) estimates that in 2005 the total prevalence of diabetes in the US was 20.8 million people or 7% of the population. This was an increase from the 2002 estimate of 18.2 million or 6.3% of the population. Nearly 10% of adults and over 20% of those 60 year of age or older have diabetes, and there has been a marked increase in the incidence and prevalence of type 2 diabetes among children and adolescents *(1)*. Both acute and chronic complications of diabetes have enormous personal and societal economic costs. Diabetes is the number one cause of adult blindness and end stage kidney disease in this country. Diabetes increases the risk for heart disease and stroke by 2- to 4-fold and is associated with many abnormalities of the nervous system collectively termed diabetic neuropathy. As a result, diabetes was estimated to account for 11% of total healthcare costs in the United States in 2002. Ninety-two billion dollars were spent on direct costs—more than double the 1997 figure of $44 billion. In 2002, indirect medical costs such as disability, work loss, or premature mortality accounted for $40 billion *(2)*.

Epidemiologic studies have clearly demonstrated the relationship between micro- and macrovascular complications and hyperglycemia as well the often accompanying hypertension and dyslipidemia. More importantly, several landmark randomized prospective clinical trials have demonstrated that improving glycemia, blood pressure (BP),

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and dyslipidemia in addition to treating the diabetes associated hypercoagulable state will reduce the risk for diabetic complications.

## DEMONSTRATED BENEFITS OF THERAPY FOR PEOPLE WITH DIABETES

### *Benefits of Improved Glycemic Control*

Several studies have demonstrated that lowering HbA1c reduces diabetes complications. The Diabetes Control and Complications Trial (DCCT), which randomized 1,441 type 1 diabetes patients to receive either intensive or conventional insulin therapy for an average of 6.5 year between 1983 and 1993, found that an improvement in HbA1c from 9.1% in the conventional group to 7.3% in the intensive treatment group was associated with a 63% decrease in retinopathy, a 54% decrease in nephropathy, and a 60% decrease in neuropathy *(3)*. Another randomized study of 110 insulin-treated type 2 patients found that, compared to conventional therapy subjects, intensively treated subjects had a lower HbA1c (7.1% compared to 9.4%), a 69% decrease in retinopathy, and a 70% decrease in nephropathy *(4)*. The United Kingdom Prospective Diabetes Study (UKPDS) reported that a reduction in HbA1c from 7.9% to 7% with intensive pharmacologic compared to conventional diet therapy was associated with a 17–21% decrease in retinopathy and a 24–33% decrease in nephropathy *(5)*.

A recent report from the DCCT-Epidemiology of Diabetes Interventions and Complications (EDIC) researchers provided follow-up information many years after the end of the DCCT. Compared to the conventional group, type 1 diabetes patients assigned to intensive treatment in the DCCT had a 42% decrease in risk for any cardiovascular outcome and a 57% reduction in the risk for nonfatal MI, stroke, or death from cardiovascular disease, even though during much of the follow-up period there was little difference in the 2 groups' HbA1c levels *(6)*. There are 2 important messages from this study. Improving glycemia will reduce the risk for macrovascular disease and, the earlier the treatment is begun, the greater the likely benefit because of an apparent metabolic memory of good and bad control.

Furthermore, in an epidemiologic analysis of the UKPDS study, researchers found that every 1% decrement in HbA1c yielded a 21% reduction in diabetes-related death, a 14% reduction in MI, and a 37% reduction in microvascular disease *(7)*.

Because better glycemic control is associated with improved clinical outcomes, lowering HbA1c may also reduce healthcare costs. UKPDS researchers calculated that the intensive therapy program cost an additional £695 per patient but was associated with a £957 reduction in the cost of complications *(8)*. An observational study by Wagner et al compared patients who exhibited a 1% decrease in HbA1c in the first or second year and maintained that decrease through a third year of the study to patients who did not have an improved HbA1c. In the subsequent 3 year, mean total healthcare costs per patient were reduced by $685 to $950 annually in the improved HbA1c group *(9)*.

Finally, data support the contention that diabetes control leads to a better quality of life. A study by Testa and Simonson compared placebo or sulfonylurea treatment for 16 week and found that compared to patients receiving placebo, patients who received pharmacologic treatment not only improved their HbA1c levels but also reported marked improvement in ratings of overall health, mental health, cognitive function, perceived health, and symptom distress *(10)*.

### *Benefits of Therapy for Dyslipidemia and Antihypertensive Therapy*

Trials of therapy with statins in patients with dyslipidemia have demonstrated that they are equally effective in those with and without diabetes. In a meta-analysis of both primary and secondary prevention trials, the relative risk for adverse cardiovascular outcomes was 0.76 while the absolute risk reductions were 2.8% and 8.0%, respectively. The number needed to treat to prevent one event was 35 in primary prevention and approx 12 for secondary prevention *(11)*. There is also evidence that reducing triglycerides and/or raising HDL-C will be associated with improved cardiovascular outcomes in those with diabetes *(12)*.

In the UKPDS a reduction of 10 mmHg systolic and 5 mmHg diastolic blood pressure was associated with a 24% reduction in any diabetes endpoint, a 37% reduction in microvascular disease, and a 32% reduction in diabetes-related deaths *(13)*. Other studies have also demonstrated the profound benefits of treatment of hypertension in those with diabetes.

### *Benefits of Comprehensive Therapy*

In the Steno-2 trial, patients with type 2 diabetes and microalbuminuria were randomized into 2 groups: one group received conventional treatment in accordance with national guidelines, and the other received intensive treatment targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, as well as secondary prevention of cardiovascular disease with aspirin. The study reported in the intensive treatment group a 53% reduction in the occurrence of macrovascular endpoints, including cardiovascular death, nonfatal myocardial infarction (MI), coronary artery bypass graft, percutaneous transluminal coronary angiography, nonfatal stroke, amputation, and bypass, as well as a 60% reduction in microvascular diseases *(14)*. This study demonstrated the importance of treating the often accompanying hypertension and dyslipidemia in type 2 diabetes patients as well as the benefits of aspirin and treatment of microalbuminuria.

## CLINICAL PRACTICE GUIDELINES FOR DIABETES MANAGEMENT

As a result of the incontrovertible evidence for the benefits of improved diabetes control, many organizations, including the American Diabetes Association; the American College of Endocrinology/American Association of Clinical Endocrinologists; the American College of Physicians; The Seventh Report of the Joint National

**Table 1**
**Recommended Clinical Practice Guidelines**

| | *ADA (15)* | *AACE (16–18)* | *ACP (19,20,21)* | *JNC 7 (22)* | *NCEP (23)* |
|---|---|---|---|---|---|
| A1C (%) | <7.0* | ≤6.5 | <7 (as low as reasonably feasible) | | |
| Fasting Glucose (mg/dL) | 70–130 | <110 | | | |
| Post-prandial Glucose (mg/dL) | <180 (peak postprandial) | <140 (2 hr postprandial) | | | |
| LDL-C (mg/dL) | <100<br>Use statin if CVD or >40 yr old with CVD RF. (optional goal <70 if CVD present) | <100;<br><70 if CVD | No specific goal; use antidyslipidemic therapy if CVD or CVD RF present | | <100 (optional goal: <70) |
| HDL (mg/dL) | Men: >40<br>Women: >50 | Men: >40<br>Women: >50 | No specific goal; use antidyslipidemic therapy if CVD or CVD RF present | | |
| Triglycerides (mg/dL) | <150 | <150 | No specific goal; use antidyslipidemic therapy if CVD or CVD RF present | | |
| Non-HDL (mg/dL) | | | | | 30 higher than LDL-C (in patients with TG ≥200) |
| Blood Pressure (mmHg) | <130/80 | <130/80 | Target blood pressure of no more than 135/80 | <130/80 | |
| Aspirin use (mg/d) | 75–162 if >40 yr of age. Consider at 30–40 yrs of age with CVD RF | Low dose ASA unless contraindications present | | | |

*The A1C goal for selected individual patients is as close to normal (<6%) as possible without significant hypoglycemia
ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists; ACP, American College of Physicians; JNC, Joint National Committee; NCEP, National Cholesterol Education Program; CV, cardiovascular; RF, risk factor

Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7); and the National Cholesterol Education Program (NCEP) have developed clinical practice guidelines to encourage physicians to improve diabetes care and outcomes by attaining and maintaining recommended treatment targets. These guidelines generally are developed by adding expert opinion to the evidence published in the medical literature (Table 1).

Although there are some differences among the guidelines, a review of the recommendations in Table 1 demonstrates that they are more similar than different. Moreover, there is little debate in the diabetes community that attainment of guideline recommendations would improve outcomes for people with diabetes.

## ACHIEVEMENT OF GUIDELINE RECOMMENDATIONS

### *Obtaining Information about Guideline Adherence*

To what degree are guideline recommendations achieved? Information about guideline adherence can be obtained from a number of sources, including the National Health and Nutrition Examination Survey (NHANES), the Behavioral Risk Factor Surveillance System (BRFSS) and the National Committee for Quality Assurance (NCQA).

The National Health and Nutrition Examination Survey (NHANES) is conducted by the National Center for Health Statistics. The program began in the early 1960s and was a series of surveys until 1999 when it became a continuous program with data released every 2 year *(24)*. It is federally funded and is designed to be representative of the US civilian, noninstitutionalized population. Samples of this population are obtained by a complex, stratified, multistage probability cluster sample design. The participants are interviewed in their homes to obtain sociodemographic, medical, and family history data, and have a physical examination and laboratory studies performed in a mobile examination center. NHANES III was the third survey conducted before it became a continuous program. It represents information gathered from 1988–1994, and is often used as the baseline for assessing progress compared to more current data sets. NHANES reports after 1999 are generally referred to using the years of data that were analyzed (i.e., NHANES 1999–2000) *(24–27)*.

Study populations for papers about patients with diabetes using NHANES data were derived using various criteria, depending on the focus of the particular study. One such population included/subjects aged 18 year and older who answered "yes" when asked whether a physician (or a health care professional in NHANES beginning in 1999) ever told them they had diabetes. Analyses of adults with diabetes generally did not include women reporting a diagnosis of diabetes only during pregnancy.

Another federally funded survey that provides evidence of rates of achievement of guideline targets is the Behavioral Risk Factor Surveillance System (BRFSS). The CDC established this program in 1984. It began with 15 state health departments participating in monthly data collection, and by 1994 included the 50 state health departments as well as those in the District of Columbia, Puerto Rico, Guam, and the U.S. Virgin Islands. It is the world's largest, on-going random-digit telephone health survey system, tracking health conditions and risk behaviors of noninstitutionalized persons in the United States each year using a standard core questionnaire. The BRFSS does not utilize physical examination or laboratory studies. Examples of information from the BRFSS used to study diabetes include data about diabetes itself, alcohol use, hypertension, obesity, physical activity, and tobacco use. Examples of study populations for papers about patients with diabetes included participants of ages 18–75 year who reported a previous diagnosis of diabetes by a healthcare professional. Women with gestational diabetes were generally excluded *(25,28)*.

### *Studies of Adherence to Diabetes Guidelines*

A few key studies from these sources demonstrate the status of adherence to guidelines for the treatment of diabetes in the United States, and particularly the progress made when comparing older data sets to more recent data.

Saydah et al *(25)* analyzed glycemic, blood pressure and cholesterol control in NHANES III compared to NHANES 1999–2000 among patients who reported a diagnosis of type 2 diabetes. There were 1,265 participants from NHANES III and 441 from NHANES 1999–2000 who were analyzed. The study found that the proportion of adults with diagnosed type 2 diabetes and an HbA1c < 7% decreased between 1988 and 2000. The percentage of patients with an HbA1c <7% declined from 44.3% in NHANES III to 35.8% in NHANES 1999-2000. The

mean A1C levels were not significantly different, with a change from 7.6 to 7.8%, and 35.8% of subjects achieved a blood pressure of <130/80 mmHg in NHANES 1999–2000 compared to 29% in NHANES III. Almost half (48.2%) of subjects had a total cholesterol <200 mg/dL, a significant increase from the 33.9% in NHANES III. Only 7.3% of those with diabetes achieved all 3 goals in NHANES 1999–2000, which represented a minimal increase compared to NHANES III.

A study of the more recent data assessing progress in the overall quality of diabetes care was published in 2006 by Saaddine et al *(25)*. Comparison of quality of diabetes care in 2 different time periods was performed using the measures of the National Diabetes Quality Improvement Alliance whenever data were available as well as some additional measures felt to be possible indicators of quality of care in the future, such as pneumococcal vaccination, diabetes education, and others. The study population included adults of ages 18–75 year who reported a previous diagnosis of diabetes by a health care professional, excluding those women who had gestational diabetes.

In this study, 1,024 participants from NHANES III and 750 participants from NHANES 1999–2002 who reported a diagnosis of diabetes and completed the clinical examination were analyzed. Participants from BRFSS 1995 (3,065) and BRFSS 2002 (13,078) who identified themselves as having diabetes were studied. The authors used data from NHANES III (1988–1994) and BRFSS data from 1995 as a baseline; the more current data were from NHANES 1999–2002 and BRFSS from 2002.

The mean HbA1c (%) was essentially unchanged, with a value of 7.8 at baseline and 7.7 more recently. The percentage of patients who were poorly controlled, with an HbA1c >9, was 24.5% in the baseline surveys and 20.6% in the recent surveys, a change that did not reach statistical significance. The ADA states that although the glycemic goal in general is a value of < 7%, the HbA1c goal for an individual patient is as close to normal (<6%) as possible without significant hypoglycemia. In the study from Saaddine et al, the proportion of patients with an HbA1c of <6%, actually decreased significantly from 23.4% to 16.4%. The proportion of participants achieving an HbA1c < 7 was not statistically different, changing from 41.3% to 42.3%. Hoerger et al studied only A1C levels from NHANES 1999–2000, 2001–2002, and 2003–2004 and found that glycemic control had steadily improved from 1999 to 2004, with a decline in mean A1C level from 7.82% in 1999–2000 to 7.18% in 2003–2004 *(29)*. The percentage of people with A1C <7% increased from 36.9% to 56.8% in the same time period, and the percentage of people who were poorly controlled with an A1C >9 decreased from 21% in 1999–2000 to 12.4% in 2003–2004. This study certainly shows a small improvement over older trends, but also demonstrates that, while most people should be able to get to goal, many (about 45%) are not.

Moreover, in the most recent survey period, only 33.8% of diabetic subjects achieved an LDL-C <100 mg/dL. Although almost 74% of individuals with diabetes achieved a diastolic blood pressure of <80 mmHg, only 48.4% had a systolic blood pressure <130 mmHg.

The "State of Diabetes in America" report released by the American Association of Clinical Endocrinologists (AACE) in 2005 demonstrated that 2 out of 3 individuals with type 2 diabetes did not achieve the HbA1c goals recommended by the ACE. The report, which analyzed a laboratory database of >157,000 people in 39 states during 2003–2004, found that 67% of patients had HbA1c levels higher than the ACE goal of ≤6.5%. In no state did more than half of the type 2 diabetic patients achieve the HbA1c goal *(30)*.

Other studies also demonstrate failure to achieve therapeutic goals among people with diabetes. Andros et al assessed blood pressure goal attainment according to JNC 7 guidelines and use of antihypertensive drug therapy in a random sample of commercial members with type 1 or type 2 diabetes in a managed care organization comprising 30 health plans across the United States *(31)*. A retrospective medical record review in October 2003 collected data from 4,814 patient charts. BP goal attainment according to JNC 7 guidelines was determined for each patient from the most recent BP reading documented in the medical chart. 751 (20.6%) of the 3,647 patients who required antihypertensive drug therapy were at JNC 7 BP goal, and 788 (21.6%) received no antihypertensive drug therapy. For the patients with DM who received antihypertensive drug therapy and had a BP value recorded in the medical chart, only 26.3% were at JNC 7 BP goal. The proportion of diabetic patients with hypertension was 59.6% ($n = 2{,}870$), and 28.4% ($n = 814$) of these patients were not taking either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB). There were 704 patients with albuminuria or nephropathy (14.6%), and 35.4% ($n = 249$) of them were taking neither an ACEI nor an ARB.

Winkelmayer et al *(32)* reported underuse of ACE inhibitors and angiotensin II receptor blockers in elderly patients with diabetes. Using linked medical claims from Medicare and the Pennsylvania Pharmaceutical Assistance Contract for the Elderly program, they studied a cohort of patients older than 65 yr with diabetes. Of 30,750 patients with diabetes studied, 21,138 patients (68.7%) also had hypertension and/or proteinuria. Of these, only 50.7% (95% confidence interval, 50.0 to 51.4) were administered an ACE inhibitor or ARB in the quarter studied. In multivariate analyses, failure to be administered either agent was associated significantly with one or more of the following: older age, male sex, chronic lung disease, depression, dementia, and other mental illness. Greater rates of ACE-inhibitor or ARB use were found in patients with coronary artery disease or congestive heart failure.

## *Why Aren't Guideline Targets Achieved?*

The failure to achieve recommended guidelines is perhaps surprising in view of the strong evidence supporting benefit from adherence and the availability of effective pharmacologic therapies for hyperglycemia, hypertension and dyslipidemia in diabetic patients. Since 1994, five new classes of oral antidiabetic agents (the biguanide metformin, thiazolidinediones, alpha glucosidase inhibitors, meglitinides, and DPP-IV inhibitors) have been introduced in this country. In addition, availability of single pill combination agents, exenatide (the 1st incretin mimetic), human insulin, premixed insulins, and rapid-acting and long-acting insulin analogs, and pramlintide acetate comprise an extensive pharmacologic armamentarium. Similarly there are many antihypertensive and antidyslipidemic agents available. Finally, the diabetes epidemic and the importance of achieving good diabetes control have been extensively reported.

The reasons for failure to achieve guideline targets include a frequent lack of optimal systems of diabetes care delivery, a failure of some clinicians to adopt a treat-to-target approach, and suboptimal adherence of some patients to both lifestyle and pharmacologic therapy.

### Suboptimal Systems of Diabetes Care Delivery

The Institute of Medicine in its publication entitled *Crossing the Quality Chasm* stated, "The healthcare system is poorly designed. Even for the most common conditions like diabetes and cancer, there are few programs that use multidisciplinary teams to provide comprehensive services for patients" *(33)*. In many if not most clinical settings, clinicians cannot easily look across their patient populations and identify individuals not attaining treatment goals. Instead, they usually wait for patients to visit and then evaluate and make therapy adjustments. If patients present with acute problems, their chronic illnesses may not be addressed. Lack of an organized system of care contributes to suboptimal diabetes control and outcomes as well as increased costs. Bodenheimer et al *(34)* and others have proposed a chronic illness care model with 6 interrelated components—self-management support, clinical information systems, delivery systems redesign, decision support, health care organization, and community resources. When this model is optimally functioning, informed patients interact with proactive practice teams to address clinical problems. The model can be applied in most practice settings – large or small, primary or specialty – and can be implemented incrementally.

Using the chronic care model, clinicians can prospectively identify patients not achieving goals so that early interventions to improve control can be implemented. Patient and clinician reminders can prompt appropriate actions. For example, Sequist et al reported that an integrated electronic reminder system resulted in definite though somewhat variable improvement in care for patients with diabetes and coronary artery disease *(35)*. The majority of physicians (76%) thought that reminders improved quality of care.

The National Diabetes Education Program (NDEP) has created the BetterDiabetesCare website, a resource designed to help practitioners better organize and deliver care to their patients with diabetes *(36)*. The BetterDiabetesCare website is focused on how to improve the way diabetes care is delivered rather than the clinical care itself. The content of the website is based on current, peer-reviewed literature and evidence-based practice recommendations. It provides models, links, resources, and tools to help assess practice needs, develop and plan strategies, implement actions, and evaluate results.

Health care professionals who use this resource can also receive continuing education credit for doing so. One can pose questions focused on improving practice: 1) How to make patient-centered team care a reality; 2) How to better manage patient notes, laboratory results, and other information; 3) How to assess the organizational status of a practice, make informed practice improvement decisions, and evaluate outcomes. Health care professionals

can then choose the tools and resources needed to find the answers, and if they document the process, for a nominal administrative fee of $10, they can receive a certificate documenting up to 10 continuing education or continuing medical education credits per year from the Indiana University School of Medicine.

There is evidence that such practice improvement interventions can have an impact on diabetes care delivery. Meigs et al *(37)* assessed a web-based decision support tool in a randomized controlled trial comparing 12 intervention and 14 control staff providers and 307 intervention and 291 control patients with type 2 diabetes in a hospital-based internal medicine clinic. The decision support tool provided patient-specific clinical data, treatment advice, and links to other web-based care resources. The number of HbA1c tests obtained per year, the number of LDL cholesterol tests, and the percentage of patients who received at least one foot examination per year all increased significantly in the intervention group. HbA1c levels decreased by 0.2% in the intervention group and increased by 0.1% in the control group ($p = 0.09$); proportions of patients with LDL cholesterol levels <130 mg/dL increased by 20.3% in the intervention group and 10.5% in the control group ($p = 0.5$). The authors concluded that web-based patient-specific decision support has the potential to improve parameters of diabetes care. However, an accompanying editorial by Dr. Patrick O'Connor *(38)* expressed disappointment that key care outcomes such as HbA1c and LDL levels did not improve more. Another study *(39)* also showed increased rates of test ordering but no improvement in metabolic parameters such as HbA1c, lipids, or blood pressure levels. Dr. O'Connor suggested that reminders to physicians would have a greater impact if they also included suggestions for specific clinical interventions for a particular patient at a particular point in time.

### Suboptimal Adherence of Patients to Lifestyle and Pharmacologic Therapy

When primary care general internists were asked in a survey conducted by the Council for the Advancement of Diabetes Research and Education (CADRE) to identify barriers to achieving optimal diabetes care, patient lack of adherence to nonpharmacologic (medical nutrition therapy and appropriately prescribed physical activity) and pharmacologic therapy were among the most frequently cited responses. The fact that almost two-thirds of American adults are overweight or obese and 30% are frankly obese *(40)* attests to the difficulty patients experience in adhering to lifestyle recommendations. Mokdad et al have demonstrated that for every kilogram increase in self-reported weight, diabetes increased by approx 9% *(41)*.

A systematic review by Cramer noted that retrospective analyses have shown that adherence to oral antidiabetic agents during clinical trials ranged from 36–93% in patients remaining on treatment for 6–24 month. Further, studies documented that patients took 67–85% of oral agent doses as prescribed and that insulin adherence among patients with type 2 diabetes was only 62–64% *(42)*.

Ho et al recently studied nonadherence in diabetes patients who were members of a private managed care organization *(43)*. The effects of medication nonadherence on hospitalization and mortality were specifically evaluated in this population, with attainment of treatment targets for HbA1c, blood pressure, and LDL-C levels as secondary outcomes. Adherence was assessed using outpatient pharmacy records to determine the proportion of days covered based on prescriptions filled. The study identified medication nonadherence in 21% of patients and found that this was associated with significantly higher HbA1c, blood pressure, and LDL-C levels. Also, nonadherent patients had significantly higher risk for all-cause hospitalization and all-cause mortality *(43)*.

The same journal issue contained several articles on adherence that identified potential harms and potential causes of nonadherence. An accompanying editorial identifies a number of challenges to adherence, suggesting changes that could improve adherence *(44)*. In particular, the judicious use of medications is advocated: prescribing the smallest possible number of medications (including taking advantage of combination pills) and the fewest doses. Improvements in systems of care to provide information on new medications at the time of prescription and to reduce medication errors at transitions of care are suggested. Decreasing the financial burden associated with some especially beneficial medications may also improve adherence *(44)*.

The DAWN (Diabetes Attitudes, Wishes, and Needs) study examined the role that psychosocial factors play in diabetes outcomes and evaluated patient-reported levels of adherence. Respondents to the survey, administered by 30 to 50 minute long structured telephone or face-to-face interviews, included physicians, nurses, and people with diabetes, totaling 5,104 adults in 11 regions in 13 countries. A study of patient reported outcomes in the DAWN project *(45)* showed an overall adherence with the recommended lifestyle regimen of 3.06 on a 4 point

scale. When compared to the U.S., the level of adherence with lifestyle recommendations was higher in 7 other countries and worse in 2. In this study, adherence to the medical regimen included the respondent's assessment of her/his success in following a combination of pharmacologic and nonpharmacologic aspects of care, such as the self-monitoring of blood glucose, medication administration, and appointment keeping recommendations given by doctors or nurses for managing diabetes. Self-reports of adherence with the recommended medical regimen were higher than lifestyle adherence, at 3.48 on the same 4 point scale overall. No country reported adherence with the medical regimen that was significantly higher than that in the US.

Polonsky et al developed the Diabetes Distress Scale as an instrument to measure diabetes related emotional distress *(46)*. It has been validated for use in both sexes and several major ethnic groups. It is a brief questionnaire for patients and identifies 4 areas of distress: emotional burden, physician-related distress, regimen-related distress, and diabetes-related interpersonal distress. Once identified, the specific concerns of a patient can be addressed by his/her clinician.

Resistance to initiation of insulin therapy is a unique adherence obstacle. Even highly motivated patients with type 2 diabetes may worry about the possibility of starting insulin therapy, as demonstrated by a survey of attendees at conferences for people with diabetes (Taking Control of Your Diabetes) *(47)*. Of respondents with type 2 diabetes who were not on insulin, 28.2% reported being unwilling to take insulin if prescribed. In a less hypothetical situation, the UKPDS, of the patients with type 2 diabetes who were randomized to insulin therapy, 28% initially refused *(48)*. This phenomenon of nonadherence with recommended treatment has been termed "Psychological Insulin Resistance." It has many factors, the major ones being, according to Polonsky and Jackson *(49)*:

- Perceived loss of control over one's life—a feeling that once insulin is started, it can never be stopped, and that it will restrict the life of the patient
- Poor self-efficacy—doubts about the patient's own ability to handle the demands and complexities of insulin therapy
- Personal failure—thought that the need for insulin therapy is the result of failure in diabetes self-care
- Perceived disease severity—perception that insulin therapy means that the disease is now more serious and more dangerous, or that insulin therapy itself will cause more health problems.
- Injection-related anxiety—fear of pain involved with injection and needle phobia (rare)
- Perceived lack of positive gain—no anticipation of improved glycemic control, energy level, or improved health

Optimal adherence cannot be achieved until these issues are addressed in each patient.

**Information Resources for Diabetes Patients.** Although a substantial amount of diabetes information can be obtained from physicians' offices, there are innumerable information resources available to patients, especially on the Internet *(50,51)*. However, much Internet information is not peer-reviewed. Patients can find valuable and creditable information from the government (e.g., National Institutes for Health, CDC, National Diabetes Education Program, MedlinePlus, etc.), not for profit disease specific sites (e.g., American Diabetes Association, Juvenile Diabetes Research Foundation), medical specialty sites (American Association of Clinical Endocrinologists, American Association of Diabetes Educators, American Heart Association) and many other web sites. A number of such web sites are listed in Table 2. Some organizations focus on assisting patients and physicians in understanding and implementing recommended diabetes care. One such organization is the National Diabetes Education Program (NDEP) *(36)*. The NDEP is a joint venture of the National Institutes of Health and the Centers for Disease Control and Prevention, together with more than 200 public and private organizations working to "change the way diabetes is treated." The NDEP has 3 major campaign efforts for which both health care professional and patient information is available on-line:

- *Control Your Diabetes for Life* – ndep.nih.gov/campaigns/ControlForLife/ControlFor/Life_index.htm
  - Includes information about *Control the ABC's (A1C, Blood Pressure, and Cholesterol) of diabetes* – ndep.nih.gov/campaigns/BeSmart/Be/Smart_index.htm
- *Small Steps, Big Rewards: Prevent Type 2 Diabetes* – ndep.nih.gov/campaigns/SmallSteps/SmallSteps_index.htm

NDEP educational materials and public service announcements are especially designed to reach the ethnic/racial groups and older adults hard hit by the diabetes epidemic. Focus group findings help NDEP develop many

**Table 2***
**Internet information resources for diabetes patients**

| | |
|---|---|
| AACE Power of Prevention | http://www.powerofprevention.com |
| American Association of Clinical Endocrinologists/American College of Endocrinology | www.aace.com |
| American Association of Diabetes Educators | www.diabeteseducator.org |
| American Diabetes Association | www.diabetes.org |
| American Dietetic Association | www.eatright.org |
| Centers for Disease Control and Prevention | www.cdc.gov/diabetes |
| Lawson Wilkins Pediatric Endocrine Society | www.lwpes.org |
| MedlinePlus | www.medlineplus.gov |
| National Diabetes Education Program | www.ndep.nih.gov |
| National Institute of Diabetes and Digestive and Kidney Diseases | www.diabetes.niddk.nih.gov |
| National Agricultural Library Food and Nutrition Information Center, US Department of Agriculture | www.nutrition.gov |
| Diabetes at work from NDEP, NBGH, NBCH, AHIP | www.diabetesatwork.org |

*Modified (used with permission) from Endocr Pract. 2006/2 (suppl 1):131–137(51).
NDEP, National Diabetes Education Program; NBGH, National Business Group on Health; NBCH, National Business Coalition on Health; AHIP, American Health Insurance Plans.

appropriate culturally sensitive materials including community partnership guides for these audiences and for health care professionals (all may be accessed via www.ndep.nih.gov, are copyright free, and can be reproduced or reprinted at no charge).

The American Diabetes Association (ADA) also has extensive information resources that can help patients to understand treatment goals and assist in achieving them (http://www.diabetes.org). ADA's initiative, Doing Better: Tools for Diabetes Care, addresses weight loss and exercise in 2 separate programs: *Weight Loss Matters*, and *Club Ped*. The ADA also has a Visit Planning Tool booklet designed to help diabetes patients better prepare for, and get more benefit from, office visits with health care professionals; it provides spaces for patients to write down questions before the visit and to keep track of their treatment goals, medications, and lab values. The Visit Planning Tool is available to health professionals for only the cost of shipping, and is appropriate for all patients with diabetes, especially the newly diagnosed.

Diabetes PHD (Personal Health Decisions https://www.diabetes.org/phd/profile/default.jsp) is an interactive internet-based risk assessment tool designed to identify the risks for developing diabetes or its complications and the effects of various health care interventions. Patients answer questions about their health and risk factors and are given their current risk for developing diabetes or diabetes microvascular, neurologic, and/or macrovascular complications. They subsequently can see the impact on their risk that could be achieved by interventions that modify their risk factors, e.g., how the risk for stroke would be changed if a patient were, to stop smoking *(52)*. The software underpinning for Diabetes PHD is Archimedes, which was developed by Kaiser Permanente with support from a grant to the ADA from Bristol-Myers Squibb Co. Archimedes is an extremely comprehensive model that simulates the biologic processes underlying the development of diabetes. The developers, Drs. David Eddy and Leonard Schlessinger, believe that no other simulation model is as comprehensive, and it is generally agreed that no other model used in medicine has been validated as extensively as Archimedes.

ACE and AACE have launched the Power of Prevention Web site (http://www.powerofprevention. com), which focuses on helping patients to understand and address key risks for diabetes and its complications, dyslipidemia, thyroid and pituitary disorders, and osteoporosis. In addition, a specific section focuses on healthier lifestyles for children; it provides extensive information for patients in a very easy-to-use format. Patients can input personal goals for health improvement and bring printouts of those goals to discuss with their physicians during appointments. AACE has used this information to develop a formal outreach program, which AACE members

are presenting in schools around the United States to promote healthy lifestyles for children and adolescents. The Power of Prevention web site has extensive nutrition information, and the Power of Prevention Guide to Physical Activity is now available.

One crucial resource that can help patients to better adhere to both non pharmacologic and pharmacologic therapy is diabetes self-management training education. Such education is ideally offered by certified diabetes educators working within an ADA recognized diabetes education program that is part of a multidisciplinary diabetes management team.

Self-monitoring of blood glucose (SMBG) is a critical skill for all diabetic patients and may help patients and their health care professionals to achieve treatment goals *(53)*. SMBG supplements the HbA1c measurement by providing timely feedback on daily glucose patterns. SMBG results show patients and their health care professionals how diet, physical activity, and medication impact blood glucose patterns. As a result, appropriate management changes can be made to better control blood glucose and thereby further reduce risk of diabetic complications.

## Failure of Clinicians to Adopt a Treat-to-Target Approach to Diabetes Management

Some clinicians may fail to take a treat-to-target approach to diabetes management. A study by Brown et al *(54)* noted that patients in their large staff model managed care organization often experienced extended periods of time with poorly controlled glycemia. Whenever patients had an HbA1c of 8.0%, their next HbA1c result was as likely to be more than 8.0 as less than 8.0%. For patients on monotherapy with either metformin or a sulfonylurea, their first HbA1c on treatment was 7.6–8.2 %, their best HbA1c on treatment was 7.1–7.7% and their last HbA1c before a change in therapy was 8.1–8.8 %. Moreover, the time interval from the best HbA1c to a change in therapy was 27–35 month. One major contributor to this clinical inertia seems to be a reluctance to initiate insulin therapy. In the study by Brown et al, the average patient had spent nearly 5 year with an HbA1c >8.0% from diagnosis until starting insulin and about 10 year with an HbA1c >7.0%.

Another barrier to optimal diabetes management is that diabetes patients usually have multiple comorbidities, each having its own set of guidelines. A paper by Boyd and Leff *(55)* examined care for older patients with multiple comorbid diseases, pointing out that half of the population older than 65 has 3 or more chronic diseases. In such cases, a balance must be struck between adhering to guidelines and individualizing treatment to patients' circumstances. Treatment of each comorbidity comes with risk and the burden of treatment on the patient and caregiver. The analysis suggested that, in some patients, following recommended guidelines of each individual disease state could result in an unsustainable treatment burden, making independent self-management and adherence difficult. Additional possible reasons for apparent nonadherence in this setting include limitations of function and of social support. A focus on those comorbidities with a shorter time to benefit and a consensus between the patient and the physician that incorporates the patient's preferences are required in this patient population *(55)*.

Data from the DAWN study reveal that, globally, the level of resistance on the part of physicians is variable, but that only in India and Japan were physicians more predisposed to delay insulin therapy than U.S. physicians *(56)*. Concern about efficacy was the factor most strongly correlated with delay of insulin therapy. Just over half of surveyed physicians and nurses agreed that insulin can have a positive impact on care. In other studies, self-blame has been identified as the attitude most predictive of patients' unwillingness to begin insulin therapy *(45)*, and physicians contribute to this perception. Over half of the health care professionals from the DAWN study reported using the threat of eventual insulin therapy as a strategy, referring to insulin as a consequence of inaction to encourage more active self-care among nonadherent patients *(56)*.

Several specific factors contributing to psychological insulin resistance on the part of the physician have been identified *(57)*:

- Sense of inadequacy or perceived inability to manage a patient's diabetes with treatments other than insulin
- A lack of adequate time or personnel to instruct a patient on how to use insulin and titrate the dose
- Concerns about weight gain and hypoglycemia
- Fear of losing or alienating the patient

Insulin therapy must be tailored to the individual patient. However, unless a physician acknowledges that the benefits of intensive control of glucose far outweigh the risks of insulin treatment, the full potential benefits of intensive glycemic control will not be realized in his/her patients.

**Resources for health care professionals.** To help address the problem of some clinicians failing to adopt a treat-to-target approach with their diabetes patients, many resources attempt to make practice guidelines more accessible to practitioners. The internet is an important resource because of its nearly ubiquitous presence in the offices of physicians. Many web sites allow clinicians to view guidelines and/or to download them to their computers or PDAs *(50,51)* . Such sites include:

- American College of Endocrinology /American Association of Clinical Endocrinologists - http://www.AACE.com
- American Diabetes Association - http://www.Diabetes.org
- BetterDiabetesCare from the NDEP - www.betterdiabeterscare.nih.gov
- Joint National Committee 7 - www.nhlbi.nih.gov/guidelines/hypertension/express.pdf
- NCEP - www.nhlbi.nih.gov/guidelines/cholesterol/index.htm
- National Guideline Clearinghouse - http://www.guideline.gov
- National Diabetes Education Program - www.ndep.nih.gov
- The Endocrine Society - http://www.endo-society.org

A need for support in decision making in the form of specific interventions at specific points of time for commonly encountered clinical situations was identified earlier in this chapter. Several therapeutic decision support resources are available as disease specific, evidence-based algorithms and suggested treatment strategies for use with individual patients at the point of care. These are not guidelines, but are tools designed to help healthcare professionals attain the goals recommended in the guidelines.

The American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) conducted an Implementation Conference for Outpatient Management of Diabetes Mellitus in 2005. A panel of diabetes experts reviewed the latest diabetes management information and adopted consensus recommendations. These included the need for clinicians to adopt an uncompromising "treat-to-target" approach to achieve and maintain glycemic goals in patients with diabetes. This approach would initiate early treatment and use persistent titration to safely achieve and maintain glycemic targets in patients with diabetes. Subsequently ACE/AACE published the Road Map for the Prevention and Treatment of type 2 diabetes. It provides guidance for the treatment of patients with type 2 diabetes who are naïve to treatment, for those who are already being treated, and for those concerned with the prevention of type 2 diabetes. For patients with established type 2 diabetes, specific interventions are suggested based on the patient's HbA1c. Persistent subsequent titration of therapy with recommended specific follow-up intervals are incorporated into the Road Map. The Road Map is easily accessible through the internet at the point of care *(58)*.

The ADA and the European Association for the Study of Diabetes (EASD) recently published a consensus statement entitled *Management of Hyperglycemia in Type 2 Diabetes: a Consensus Algorithm for the Initiation and Adjustment of Therapy.* Background information is provided, including principles in selecting antihyperglycemic interventions and a description of all of the currently available pharmacologic options. There is a specific algorithm for treatment of type 2 diabetes, beginning at the time of first diagnosis, and there is another algorithm dedicated to initiation of insulin. Suggestions include rates of titration of medications and treatment modifications based on self-monitored blood glucose and HbA1c. A quick path is drawn through oral medications to insulin if goals are not achieved *(59)*.

Another very comprehensive set of algorithms has been developed by the Texas Diabetes Council. This organization has covered several areas of comprehensive diabetes care. Suggestions are offered for achieving glycemic control in type 2 diabetes in children and adults from the time of diagnosis with a separate algorithm dedicated to insulin therapy. In addition, there are algorithms for lipid and blood pressure management as well as medical nutrition, weight loss, and other conditions. These algorithms are also available on-line at the point of care at www.dshs.state.tx.us/diabetes to assist in real-time decision making *(60)*.

Many believe that realignment of financial incentives is critical to improving clinician adherence to treatment guidelines and motivating treat-to-target diabetes management. One somewhat controversial approach has been the movement toward "pay for performance" programs by managed care organizations and other payers. These

programs use specific quality measures developed by such organizations as the National Committee for Quality Assurance (NCQA), the AMA, and the National Diabetes Quality Improvement Alliance to evaluate and provide financial incentives to health care professionals who demonstrate improved patient care processes and/or outcomes as judged by achievement of performance measures. Performance measures differ from but are also in part derived from clinical guidelines. However, performance measures must account for differences in individual patient conditions and preferences, feasibility of data collection, and accountability by the user. Although guidelines are designed to direct patient care, performance measures are designed for internal quality improvement in a physician's practice and for public reporting of quality assessment. Some examples of the Alliance's performance measures for public reporting are the percentage of diabetic patients of age 18–79 year with one or more HbA1c tests and the percentage of patients with most recent HbA1c level >9.0% within the reporting year *(61)*.

Bridges to Excellence *(62)* is an example of a pay for performance program designed to create significant improvements in the quality of care by recognizing and rewarding health care professionals who demonstrate that they have implemented comprehensive management of patients and deliver safe, timely, effective, efficient, and patient-centered care. Diabetes Care Link is one of the individual programs comprising the Bridges to Excellence initiative. Physicians who demonstrate high levels of diabetes care performance are eligible for incentive bonuses paid by participating employers. A General Electric-led employer group that includes NCQA among its charter members and a diverse coalition of physicians, health plans, quality experts, and consultants has advanced the Bridges to Excellence pay-for-quality concept. Charter employers include General Electric, Ford Motor Company, UPS, Procter & Gamble, and Verizon. The Bridges to Excellence programs offer bonus payments to physicians who deliver high-quality care to their employees in geographic areas where these programs are operational. The NCQA selects which physicians qualify for awards based on evaluating and verifying physician submitted data. Qualifying physicians could see income gains of up to 10%. In addition, participating physicians are highlighted in provider directories. One can find additional information about this program at www.bridgestoexcellence.org.

### Cost of Care Issues

Another financial impediment to optimal diabetes control is the cost of care to patients. For some patients the cost of medical visits and medications can be challenging. Yet of the $132 billion of excess costs attributable to diabetes in 2002 *(2)*, medications and supplies contributed only14% and outpatient care contributed 15%. The largest contributions to cost were institutional care like hospitalization and indirect costs, including premature mortality and absenteeism. One could make an argument that prospectively spending more for medications, supplies, and outpatient care would likely be cost saving in the future.

A recent paper by Mahoney *(63)* supports this hypothesis. Dr. Mahoney at Pitney Bowes offered an innovative approach to management of the pharmacy benefit for company employees with diabetes. By shifting diabetes medications from tier 2 or 3 formulary status to tier 1, potential financial disincentives to patient's use of diabetes medications and supplies were significantly diminished. The result was an increase in medication possession rates, a marker of adherence, a decrease in total per-patient pharmacy costs, a 6 % decrease in costs per employee with diabetes and a slowing of the increases in overall per-patient medical costs. The company simultaneously implemented other diabetes disease management activities, including distribution of free glucose meters to employees with diabetes, which could have contributed to the observed improvement in costs. However, the author contended that benefit redesign was the truly novel component of their efforts.

## *New Therapies*

Although success at achieving guideline targets should be much better with present therapies, the addition of new therapies may well help more patients to get to target. Present therapies have many benefits but still fail to address unmet needs. Many therapies are associated with hypoglycemia and weight gain. Postprandial hyperglycemia and excessive glycemic fluctuations frequently remain a problem even when present therapies achieve good HbA1c levels. There is gradual loss of glycemic control related to progressively declining beta cell function in type 2 patients with most present therapies. Finally, although many type 2 diabetes patients would benefit from initiating insulin therapy, often they and their health care professionals are reluctant to do so. Concern about injection is one of the reasons for this reluctance. Newly available therapies including GLP-1

related agents, and therapies under development such as inhaled insulin and protein kinase C inhibitors offer the potential to address some of these unmet needs.

## CONCLUSIONS

Many diabetic patients do not achieve treatment goals that have been proven to reduce the risk of micro- and macrovascular complications. Some of the reasons for the lack of adherence to guidelines have been reviewed in this chapter. The development of evidence-based guidelines, increasing awareness of those guidelines, incentives to motivate both patients and clinicians, programs to support physicians and patients in reaching the goals of therapy, and optimal use of therapies and health care delivery systems are all needed to realize improvement in diabetes care for the 20.8 million Americans with diabetes and the increasing number who will develop diabetes in the future.

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# 16 Treatment of Hypertension in Type 2 Diabetes

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***Contents***



**Summary**

High blood pressure is a common coexisting condition in patients with type 2 diabetes mellitus, affecting over a third of adults with diabetes. The presence of high blood pressure increases the risk of numerous macro- and micro-vascular complications of diabetes, including cardiovascular disease, nephropathy, retinopathy, and possibly, neuropathy, and the association of blood pressure with complications extends into the blood pressure range usually considered normal in persons without diabetes. The relative increase in risk attributable to high blood pressure is comparable in persons with and without diabetes, but the combination of high baseline risk of complications in patients with diabetes and this relative risk generate a much larger absolute excess risk of high-blood-pressure-related complications in persons with diabetes than in those without. Clinical trial data have proven the benefits of blood pressure lowering therapy in patients with diabetes; however, the most appropriate goal for the treated blood pressure level is unknown. The clinical trial evidence clearly supports systolic blood pressure levels less than 150 mm Hg and diastolic blood pressure levels less than 80 mm Hg. Lower systolic blood pressure goals are supported by observational data. The relative benefits of various blood pressure lowering medications has received much attention and generated much controversy. Because most patients with diabetes will require triple drug therapy with a diuretic, ACE inhibitor (or angiotensin receptor blocker), and calcium channel blocker to achieve blood pressure control, this debate is largely academic. In patients with high blood pressure but not diabetes, the risk of developing diabetes may be reduced by ACE inhibitors, angiotensin receptor blockers and calcium channel blockers relative to diuretics and beta-blockers. Prevention of diabetes and high blood pressure remain important long-term public health goals; however, given the frequency and complications of high blood pressure in patients with diabetes, and the proven benefits of blood pressure control, attention to improving the quality of care for high blood pressure in patients with diabetes is of major importance.

**Key Words:** High blood pressure; diabetes; cardiovascular disease; nephropathy; retinopathy; neuropathy; diuretics; ACE inhibitors; angiotensin receptor blockers; beta-blockers; calcium channel blockers; treatment recommendations; prevention.

## RISKS OF HIGH BLOOD PRESSURE IN TYPE 2 DIABETES

High blood pressure is a common medical problem in patients with type 2 diabetes. According to results from the National Health and Nutrition Examination Survey (NHANES) 1999–2000, 31% of men and 43% of women with diabetes in the United States (US) had high blood pressure *(1)*. These high prevalence figures contrast with 28.3% of all men and 28.7% of all women in the US *(2)*. In addition, diabetes has been shown to increase the incidence of high blood pressure by approx 50% *(3)*. This increased risk may be caused by mechanisms related to

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insulin resistance *(4)* and hyperinsulinemia *(5–7)*, including effects on salt sensitivity, the nocturnal fall in blood pressure *(8)*, the response of blood pressure to exercise *(9)*, and left ventricular mass and structure *(10)*.

High blood pressure is an important risk factor for the major forms of cardiovascular disease (CVD), including coronary heart disease, heart failure, stroke, and peripheral arterial disease *(11)*. CVD is the leading cause of death and a major cause of morbidity in the US, regardless of diabetes status *(11)*. The adverse effect of high blood pressure on risk of coronary heart disease and stroke has been recognized for several decades *(12)*, and for over a decade in persons with diabetes *(13)*. The risk of major CVD events increases in a continuous manner across the distribution of blood pressure *(14)*. In patients with type 2 diabetes, there is also a graded increase in risk for CVD and microvascular complications across the entire range of blood pressure levels, including blood pressure levels below current treatment thresholds *(13,15,16)*. Among 347,978 middle-aged men screened for participation in the Multiple Risk Factor Intervention Trial (MRFIT), the absolute risk of CVD mortality increased more steeply across progressively higher systolic blood pressure (SBP) categories among men with diabetes than among men without diabetes *(13)*. Consequently, as shown in Table 1, the absolute excess risk of CVD mortality attributable to higher blood pressure was much greater in men with diabetes than in men without diabetes, regardless of serum total cholesterol concentration or cigarette smoking status *(13)*. In the observational component of the United Kingdom Prospective Diabetes Study (UKPDS), higher baseline and subsequent SBP levels were associated with greater relative and absolute risk of total mortality, deaths, and complications related to diabetes, including CVD events and microvascular complications (Table 2) *(15)*.

Stroke is the third leading cause of death and a major cause of morbidity in the US in persons with and without diabetes *(11)*. At the population level, high blood pressure is probably the most important risk factor for stroke; nevertheless, diabetes and high blood pressure each independently increase the risk of stroke *(17–20)*. Little evidence exists regarding the precise nature of the association between blood pressure and the risk of stroke in patients with diabetes; however, Hu et al reported that the effect of high blood pressure on risk of stroke was similar among persons with and without diabetes *(21)*. It seems prudent to presume that the continuous relationship observed between blood pressure and risk of stroke in persons without diabetes *(14)* exists in persons with diabetes. Consequently, given the greater absolute risk of stroke in patients with diabetes versus those without, the excess risk of stroke related to high blood pressure is likely to be much greater in people with diabetes than in those without diabetes.

Heart failure is a major public health problem in people with diabetes. Bertoni, et al. reported a prevalence of heart failure of 22% in Medicare beneficiaries with diabetes; in addition, the incidence of heart failure was 12.6 per 100 person-years *(22)*. In the general population of people $\geq 65$ yr old, the prevalence of heart failure is less

**Table 1**
**Relative and absolute risks for cardiovascular disease (CVD) mortality associated with systolic blood pressure (SBP) below or at least 120 mm Hg in men with and without diabetes according to serum total cholesterol concentration and cigarette smoking status at initial screening for the Multiple Risk Factor Intervention Trial**

| *Diabetes* | *Serum Cholesterol (mg/dL)* | *Cigarette Smoking* | *Age-adjusted CVD Mortality (per 10,000 person-years)* | | *Relative Risk (≥ 120/<120 mm Hg)* | *Excess Risk(≥ 120 mm H - < 120 mm Hg [per 10,000 person-years])* |
|---|---|---|---|---|---|---|
| | | | *SBP < 120 mm Hg* | *SBP ≥ 120 mm Hg* | | |
| No | < 200 | No | 6.02 | 12.96 | 2.15 | 6.94 |
| Yes | < 200 | No | 30.68 | 60.33 | 1.97 | 29.65 |
| No | < 200 | Yes | 14.33 | 28.50 | 1.99 | 14.17 |
| Yes | < 200 | Yes | 57.12 | 102.71 | 1.80 | 45.59 |
| No | 200+ | No | 9.99 | 20.59 | 2.06 | 10.6 |
| Yes | 200+ | No | 52.17 | 87.03 | 1.67 | 34.86 |
| No | 200+ | Yes | 23.48 | 47.38 | 2.02 | 23.90 |
| Yes | 200+ | Yes | 86.01 | 125.23 | 1.46 | 39.22 |

Modified from reference *(15)*.

**Table 2**
**Adjusted* relative risk increment associated with a 10 mm Hg greater systolic blood pressure (SBP), measured at baseline and as an updated mean, among 3642 participants in the observational component of the United Kingdom Prospective Diabetes Study**

| | | *Baseline SBP* | | *Updated Mean SBP* | |
|---|---|---|---|---|---|
| *Endpoint* | *Number of Events* | *Relative Risk Increment (%)* | *95% CI (%)* | *Relative Risk Increment (%)* | *95% CI (%)* |
| Total mortality | 597 | 13 | 10, 17 | 12 | 9, 16 |
| Diabetes related deaths | 346 | 19 | 15, 23 | 17 | 13, 21 |
| Diabetes complications | 1255 | 9 | 7, 12 | 12 | 9, 14 |
| Microvascular disease | 323 | 10 | 4, 15 | 13 | 9, 26 |
| Myocardial infarction | 496 | 13 | 9, 16 | 12 | 7, 16 |
| Heart failure | 104 | 14 | 5, 21 | 15 | 4, 19 |
| Stroke | 162 | 13 | 7, 19 | 19 | 14, 24 |
| Peripheral arterial disease | 41 | 30 | 20, 39 | 16 | 9, 23 |

*Adjusted for age at diagnosis of diabetes, sex, ethnicity, smoking, microalbuminuria, hemoglobin A1c, high and low density cholesterol, and triglycerides. Modified from reference *(17)*.

than 10% *(11)*; a difference that underscores the effect of diabetes on heart failure risk. The independent roles of high blood pressure and diabetes in the etiology of heart failure have been recognized for at least 2 decades *(23)*; however, early research on heart failure etiology and prevention focused primarily on high blood pressure, perhaps because the relative risk for heart failure was greater for high blood pressure than for diabetes and because high blood pressure was much more common than diabetes. Recent research has documented a continuous relationship between blood pressure and heart failure risk. For example, in the Framingham Heart Study, a 20 mm Hg greater SBP was associated with a 56% greater risk for heart failure *(24)*. As is the case with stroke, limited evidence exists regarding the precise nature of the association between blood pressure and risk of heart failure in people with diabetes; however, Iribarren et al. showed no interaction between blood pressure and hemoglobin A1c on risk of heart failure *(25)*. It seems likely that the continuous relationship exists in patients with diabetes as well as in those without. The excess risk for heart failure caused by higher blood pressure levels is likely to be much greater in persons with diabetes given their greater absolute risk of heart failure, even at optimal blood pressure levels, when compared with persons without diabetes.

Diabetes and high blood pressure are the top 2 causes of end-stage renal disease in the US *(26)*. The incidence of chronic renal failure in diabetes has been estimated to range between 133 per 100,000 person-years in Rochester, Minnesota *(27)* to 200 per 100,000 person-years among MRFIT screenees *(28)* to 1570 per 100,000 person-years among Oklahoma Indians *(29)*. Diabetes increased the risk of end-stage renal disease by a factor of almost 10 (RR, 9.0; 95% CI, 7.4–11.0) among MRFIT screenees *(28)*. The clinical diagnosis of high blood pressure is reported to double the risk of nephropathy in patients with diabetes *(29)*; however, the relationship is probably continuous in nature. Among 332,544 men who were screened for entry into the MRFIT, a strong gradient was observed between baseline blood pressure level and risk of end-stage renal disease. As compared with men with an optimal level of blood pressure (systolic pressure $< 120$ mm Hg and diastolic pressure $< 80$ mm Hg), the relative risk of end-stage renal disease for those with stage 4 hypertension (systolic pressure $= 210$ mm Hg or diastolic pressure $= 120$ mm Hg) was 22.1 ($p < 0.001$) *(30)*. The excess risk of end-stage renal disease caused by higher blood pressure is certainly greater in patients with diabetes than in those without. Even after adjustment for baseline glomerular filtration rate, which is probably influenced by high blood pressure and diabetes, Fox, et al. reported elevated odds ratios for development of new onset kidney disease attributable to diabetes (2.6) and high blood pressure (1.6), based on data from the Framingham Heart Study *(31)*.

In the US, diabetic retinopathy is the fifth most common cause of legal blindness and occurs in about 4.8 people per 100,000 population *(32)*. Higher blood pressure increases the risk of retinopathy in patients with diabetes *(33–38)*. In the Barbados Eye Study, the relative risk (RR) for diabetic retinopathy increased by 30% for every

10 mm Hg higher SBP at baseline (RR, 1.3; 95% CI, 1.1–1.4). This relationship was observed even within the normal range for blood pressure. A 10 mm Hg increase in SBP from baseline to the 4-yr follow-up was associated with a similar increase in risk (RR, 1.3; 95% CI, 1.1–1.4) *(33)*. In a study of Pima Indians, the incidence of exudates in those with SBP of at least 145 mm Hg was more than twice that of those with SBP of less than 125 mm Hg *(34)*. In the San Luis Valley Diabetes Study, the RR for retinopathy was 80% greater for a 20 mm Hg higher SBP *(37)*.

The risk of diabetes related neuropathy, for autonomic *(39)*, peripheral sensory neuropathy, *(40)* and composite definitions *(41)*, has been associated with hypertension in patients with type 1 diabetes, but evidence regarding this relationship in type 2 diabetes is sparse and inconsistent. Cohen, et al., reported an association between high blood pressure and sensory, but not autonomic, neuropathy in patients with type 2 diabetes, based on data from the Appropriate Blood Pressure Control in Diabetes Trial *(42)*. In contrast, high blood pressure was not associated with risk of sensory neuropathy in patients with type 2 diabetes in the San Luis Valley Diabetes Study *(43)*. At present, the role of high blood pressure in the etiology and progression of diabetes-related neuropathy is unclear.

In summary, type 2 diabetes is associated with increased risk for numerous macrovascular and microvascular complications. The risk for all of the complications reviewed above, with the possible exception of neuropathy, is increased in the presence of high blood pressure. As a consequence of the multiplicative nature of the interaction between diabetes and high blood pressure, the excess risk attributable to high blood pressure is much higher in patients with diabetes than in patients without diabetes. Therefore, it would seem reasonable to expect that treatment of high blood pressure would be especially effective in reducing the absolute risk of these complications in patients with diabetes.

## BENEFITS OF BLOOD PRESSURE CONTROL IN TYPE 2 DIABETES

As reviewed above, the increase in CVD risk associated with higher blood pressure is independent of the increase in CVD risk associated with diabetes; therefore, diabetes and hypertension combined confer a much higher risk than either alone *(13)*. In part because of this higher risk, observed even in the prehypertensive range, the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended beginning drug treatment at lower blood pressure levels in patients with diabetes than in patients without diabetes. In patients with diabetes, blood pressure lowering treatment is recommended when the systolic blood pressure (SBP) is $\geq 130$ mm Hg or the diastolic blood pressure (DBP) is $\geq 80$ mm Hg, with treatment goals of $< 130/80$ mm Hg *(16)*. However, there is a paucity of randomized clinical trial evidence to support these recommendations. The 2004 Veterans Affairs-Department of Defense (VA-DoD) hypertension guidelines, relying primarily on available evidence from clinical trials, recommend a goal blood pressure in diabetes mellitus of $< 140/80$ mm Hg *(44)*. Table 3 provides summary information from randomized clinical trials regarding the effect of blood pressure lowering treatment on risk of CVD endpoints.

The Systolic Hypertension in the Elderly Program (SHEP) was designed to test the hypothesis that treatment of isolated systolic hypertension would reduce the risk of stroke and CVD in elderly persons *(45)*. In the overall SHEP population, stroke was reduced by 36% and major CVD by 32% by chlorthalidone-based therapy *(46)*. In a *post hoc* subgroup analysis of participants with type 2 diabetes in SHEP, major CVD events were reduced by 34% *(47)*. Whereas the relative risk reduction was similar in participants with and without diabetes, the absolute risk reduction was twice as great in participants with diabetes as in those without. The Systolic Hypertension in Europe (Syst-Eur) Trial, was a similar trial conducted in Europe but using nitrendipine as the initial blood pressure lowering drug *(48)*. Stroke was reduced by 42% and CVD by 31% *(49)*. Patients with diabetes were reported in a *post hoc* subgroup analysis to have significant reductions in total mortality (55%), CVD mortality (76%), all CVD events (69%), and stroke (73%) *(50)*.

The Hypertension Optimal Treatment (HOT) study was designed to test the relative effectiveness of treatment to 3 different DBP goals ($= 90$, $= 85$, and $= 80$ mm Hg) on risk of CVD *(51)*. Participants in the more intensively treated group received ACE inhibitors, beta-blockers, and diuretics more often than did the less intensively treated participants; however, there was little difference in use of felodipine (the initial therapy used per protocol). No difference in CVD event rates was observed between the treatment groups in the overall study population *(52)*. In a *post hoc* analysis of participants with diabetes, major CVD events were reduced by 51% ($p = 0.005$) among

**Table 3**
**Clinical trials of blood pressure lowering in patients with diabetes**

| *Trial* | *N* | *Duration* | *Mean BP, less intense* | *Mean BP, more intense* | *Initial Therapy* | *Outcome* | *Relative Risk Reduction* |
|---|---|---|---|---|---|---|---|
| SHEP[88] | 583 | 5 yr | 155/72* | 146/68* | Chlorthalidone | Stroke | 22% (ns) |
| | | | | | | CVD events | 34% |
| | | | | | | CHD | 56% |
| Syst-Eur[89] | 492 | 2 yr | 162/82 | 153/78 | Nitrendipine | Stroke CV events | 69% |
| | | | | | | CV events | 62% |
| HOT[90] | 1, 501 | 3 yr | 148/85 | 144/81 | Felodipine | CV events | 51% |
| | | | | | | MI | 50% |
| | | | | | | Stroke | 30% (ns) |
| | | | | | | CV mortality | 67% |
| UKPDS[92] | 1, 148 | 8.4 yr | 154/87 | 144/82 | Captopril or atenolol | Diabetes-related endpoints: | 34% |
| | | | | | | Deaths: | 32% |
| | | | | | | Strokes | 44% |
| | | | | | | Microvascular | 37% |
| ABCD[94] | 470 | 5.3 yr | 138/86 | 132/78 | Nisoldipine or enalapril | $C_{Cr}$ | nc |
| | | | | | | Albuminuria | nc |
| | | | | | | Retinopathy | nc |
| | | | | | | Neuropathy | nc |
| | | | | | | Mortality | 49% |
| | | | | | | MI, Stroke, CHF | ns |

BP, blood pressure; C , Creatine Clearance; CHD, Coronary heart disease; CHF, Congestive heart failure; CV, Cardiovascular; CVD, Cardiovascular Disease; MI, Myocardial infarction.
nc = no change
ns = not significant
*Personal communication from Sara Pressel, School of Public Health, University of Texas Health Science Center.

those randomized to a DBP goal of = 80 mm Hg compared to a goal of = 90 mm Hg *(52)*. The large size of the observed treatment effect in participants with diabetes was impressive. However, the number of major CVD events observed in participants with diabetes was relatively small ($n$ = 101), and the difference between the blood pressure achieved for the more intensively treated participants with diabetes (144/81 mm Hg) compared with the less intensively treated group (148/85 mm Hg) was small (4/4 mm Hg) *(53)*. Furthermore, as indicated above, no difference in CVD event rates was observed between randomized groups in the entire HOT population despite an identical difference in achieved blood pressures. The authors did not report how many subgroup analyses they examined; hence, the role of chance can not be completely excluded.

In the UKPDS, hypertensive patients with type 2 diabetes were randomized to more or less intensive blood pressure control (goals < 150/85 versus < 180/105 mm Hg). Participants randomized to more intensive control were also randomized to initial therapy with either captopril or atenolol. The suggested sequence for adding medications was furosemide, slow release nifedipine, methyldopa, and prazosin. Nifedipine was the agent used most often in the less intensively treated group. Average blood pressure over 9 yr was 144/82 and 154/87 mm Hg in the more and less intensively treated groups, respectively. In the more intensively treated group, 29% of participants were taking at least 3 drugs, just over 30% were taking 2 drugs, and fewer than 40% were taking 1 or 0 drugs. Diabetes related endpoints were reduced by 24% (95% CI, 8% to 38%; $p$ = 0.005), deaths related to diabetes by 32% (95% CI, 6–51%; $p$ = 0.019), strokes by 44% (95% CI, 11–65%; $p$ = 0.013), and microvascular endpoints by 37% (95% CI, 11–56%; $p$ = 0.009) with intensive therapy to reduce blood pressure *(54)*. Although not statistically significant, all-cause mortality was lower by 18% and myocardial infarction by 21%.

The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial, a prospective, randomized, blinded trial in hypertensive patients with diabetes, compared the effects of moderate control of blood pressure (target DBP

80–89 mm Hg) with those of intensive control (DBP 75 mm Hg or less) on the incidence and progression of diabetes related nephropathy, retinopathy, cardiovascular disease, and neuropathy *(55–57)*. Therapy was based on use of nisoldipine and enalapril. The mean blood pressure achieved in the intensive group was 132/78 mm Hg versus 138/86 mm Hg in the moderate control group. There were no differences in any microvascular endpoints for the 2 BP goals. The intensive therapy group had a lower mortality rate (5.5% versus 10.7%, $p = 0.037$), but there were no statistically significant differences in myocardial infarction, cerebrovascular events, or heart failure to account for the mortality difference.

The HOT and UKPDS studies provide the most definitive clinical trial evidence to date and support BP goals of < 150/85 mm Hg (UKPDS) and DBP < 80 mm Hg (HOT) in patients with both hypertension and diabetes. These goals and the achieved BP levels in these and other trials are consistent with an SBP goal of 140 mm Hg in patients with diabetes. No trials, including ABCD, have confirmed CVD benefits of treating to lower BP goals. In particular, no trial has tested whether reduction to "optimal" levels as defined by JNC 7 (i.e., SBP < 120 mm Hg) would provide additional CVD benefits. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial was designed to provide evidence relevant to this question. Of the 10,251 participants in ACCORD, 4,733 were randomized in a factorial substudy examining the effects of an intensive blood pressure lowering strategy, targeting a SBP < 120 mm Hg, versus a standard strategy, targeting a SBP < 140 mm Hg. The primary outcome measure for the trial is the first occurrence of a major cardiovascular event, specifically nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Participants will be followed for 4–8 yr (Mean 5.6 yr), and follow-up is planned to continue through the summer of 2009 *(58)*.

## RELATIVE EFFICACY OF VARIOUS CLASSES OF BLOOD PRESSURE LOWERING MEDICATIONS

The best choice of pharmacologic therapy for lowering blood pressure has been a much debated topic, both for persons with and without diabetes. Multiple clinical trials have been conducted to compare various antihypertensive agents to placebo or to other active comparators. Metabolic considerations have been discussed to support the use of newer agents (e.g., ACE inhibitors, alpha-adrenergic receptor blockers, angiotensin receptor blockers, and calcium channel blockers) with potentially fewer detrimental effects than older agents on electrolyte concentrations (thiazide-type diuretics), lipid and lipoprotein concentrations (thiazide-type diuretics and beta-adrenergic receptor blockers), and glucose and insulin metabolism (thiazide-type diuretics and beta-adrenergic receptor blockers). Several recent trials and meta-analyses have contributed important information relevant to this issue.

Psaty, et al., reported the results of a meta-analysis of 42 clinical trials testing 7 major treatment strategies (placebo, ACE inhibitors, alpha-blockers, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and low-dose diuretics) involving 192,748 participants with and without diabetes *(59)*. None of the alternative agents was superior to low-dose diuretics (the equivalent of 12.5 to 25 mg /d of chlorthalidone or 25–50 mg /d of hydrochlorothiazide) for any of the outcomes examined (coronary heart disease, heart failure, stroke, CVD events, CVD deaths or total mortality). Low-dose diuretics were superior to ACE inhibitors for heart failure, CVD events and stroke; to alpha-blockers for heart failure and CVD events; to beta-blockers for CVD events; and to calcium channel blockers for heart failure and CVD events. Blood pressure effects were similar between active agents *(59)*. No results were reported specific to patients with diabetes.

The Blood Pressure Lowering Treatment Trialists' Collaboration reported the results of a prospectively planned meta-analysis of 29 randomized trials involving 162,341 participants, and reported results similar to those of Psaty. Neither of the newer agents examined (ACE inhibitors and calcium channel blockers) were superior to the older agents examined (beta-blockers or diuretics) for any of the outcomes examined (coronary heart disease, heart failure, stroke, CVD events, CVD death, or total mortality). The older agents were superior to ACE inhibitors for stroke and to calcium channel blockers for heart failure and CVD events *(60)*. A subsequent meta-analysis by this collaboration from the same database reported drug comparisons in hypertensive patients with and without diabetes *(61)*. They concluded that "the short- to medium-term effects on major cardiovascular events of the BP-lowering regimens studied were broadly comparable for patients with and without diabetes." Two limitations of these meta-analyses are: 1) there are no separate analyses using diuretics alone as a comparator group (diuretics

were superior to beta-blockers in several trials and other meta-analyses), and 2) many studies were excluded because it was a prospective meta-analysis.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) randomized over 42,000 participants to 1 of 4 active antihypertensive agents: chlorthalidone (a thiazide-type diuretic), amlodipine (a calcium channel blocker), doxazosin (an alpha blocker), and lisinopril (an ACE inhibitor). The primary outcome measure was the combined occurrence of fatal coronary heart disease (CHD) or nonfatal myocardial infarction, analyzed by intent to treat. The doxazosin arm was terminated early, after a mean follow-up of 3.2 yr owing to a higher risk of stroke (RR, 1.26; 95% CI, 1.10–1.46) and combined CVD (RR 1.20; 95% CI, 1.13–1.27) in all participants *(62)*.

The 3 other arms in ALLHAT continued until the planned termination of the trial, following a mean follow-up of 4.9 yr. Overall, there was no difference in the primary endpoint or all cause mortality between the treatment groups; however, in comparison to chlorthalidone, amlodipine was associated with greater incidence of heart failure (RR, 1.38; 95% CI, 1.25–1.52), and lisinopril was associated with greater risk of stroke (RR, 1.15; 95% CI, 1.02–1.30), combined CVD (RR, 1.10; 95% CI, 1.05–1.16), and heart failure (RR, 1.19; 95% CI, 1.07–1.31) *(63)*. Similar results were observed in the subgroup of patients with diabetes. Amlodipine was associated with greater risk of heart failure (RR, 1.42; 95% CI, 1.23–1.64), and lisinopril was associated with greater risk of combined CVD (RR 1.08; 95% CI, 1.00–1.17) and heart failure (RR, 1.22; 95% CI, 1.05–1.42). These findings in favor of chlorthalidone were seen despite the expected lesser decreases in total cholesterol and greater increases in fasting glucose and greater decreases in potassium among participants assigned to chlorthalidone *(63)*. A more extensive analysis of the ALLHAT data by diabetes status, published by Whelton, et al., confirmed these results and showed no evidence of a benefit of therapy with amlodipine or lisinopril versus chlorthalidone in patients with diabetes *(64)*. Whereas the estimated glomerular filtration rate was preserved more effectively by amlodipine and lisinopril than by chlorthalidone *(63)*, there was no difference between the treatment groups in the development of end-stage renal disease, regardless of DM status *(65)*. In comparison to the chlorthalidone-treated group, the relative risk of developing end-stage renal disease in participants with diabetes was 1.30 (95% CI, 0.98–1.73) for amlodipine-treated participants and 1.17 (95% CI, 0.87–1.57) for lisinopril-treated participants *(65)*. Large beneficial effects of amlodipine or lisinopril relative to chlorthalidone on development of end-stage renal disease in patients with diabetes are not consistent with these findings.

The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) tested the relative efficacy of atenolol with bendroflumethiazide (a thiazide-type diuretic) added if needed versus amlodipine with perindopril added if needed, and the study was stopped early. The investigators reported a significant reduction in fatal and nonfatal stroke (RR, 0.77; 95% CI 0.66–0.89), total cardiovascular events and procedures (RR, 0.84; 95% CI 0.78–0.90), and all-cause mortality (RR, 0.89; 95% CI, 0.81–0.99) in the amlodipine/perindopril group *(66)*. There was not a statistically significant difference between groups in the primary endpoint (nonfatal myocardial infarction [including silent myocardial infarction] and fatal CHD). Reductions in total cardiovascular events and procedures were similar for participants with diabetes (RR, 0.87; 95% CI, 0.76–0.99) and without diabetes (RR, 0.82; 95% CI, 0.75–0.90), suggesting that the relative superiority of amlodipine over atenolol is similar across both subgroups *(66)*. However, it is difficult to compare the ASCOT findings to those from previous outcome trials for several reasons: the addition of agents from different antihypertensive classes to the 2 treatment arms makes it impossible to determine whether one or the combination of both might be responsible for beneficial cardiovascular outcomes; the thiazide dose used in the trial is ¼ to ½ the dose used in prior trials.

The effect of different blood pressure lowering medications on renal function has received great attention in patients with type 2 diabetes *(67–85)*. Overwhelming evidence supports the effectiveness of ACE inhibitors and angiotensin receptor blockers in slowing the progression of microalbuminuria and preventing the development of overt nephropathy *(67–85)*. The relative superiority of these medications over blood pressure lowering medications from other classes has been less well studied. Some studies have shown relative equivalence of ACE inhibitors and calcium channel blockers *(69,81)*; whereas, others have shown superiority of ACE inhibitors over calcium channel blockers *(79,82)*. Irbesartan was superior to amlodipine in the Irbesartan Diabetic Nephropathy Trial *(84)*. In addition, ramipril was superior to atenolol in one trial *(72)*. Combined use of ACE inhibitors and angiotensin receptor blockers was superior to monotherapy with either alone in some *(75,83)* but not *(85)* all trials. Similarly, whereas a trial of the combination of amlodipine and fosinopril demonstrated superiority of combination therapy

over either monotherapy *(79)*, a trial of the combination of trandolapril and verapamil showed no benefit of adding verapamil to trandolapril or even of verapamil versus placebo *(82)*. Based on this evidence, it may be reasonable to prefer ACE inhibitors or angiotensin receptor blockers in the presence of microalbuminuria; however, this evidence should be considered along with the results of ALLHAT, described above, that showed no superiority of lisinopril over chlorthalidone in the development of end-stage renal disease in patients with high blood pressure and type 2 diabetes *(65)*.

## DIABETES PREVENTION WITH ANTIHYPERTENSIVE AGENTS

The potential role of antihypertensive agents to prevent the development of diabetes has also received attention. In the Captopril Prevention Project (CAPPP), the effect of therapy based on the ACE inhibitor captopril was compared with conventional treatment, consisting of beta-blockers and diuretics. Atenolol and metoprolol were the most commonly used -blockers, and hydrochlorothiazide and bendrofluazide were the most commonly used diuretics. There was no difference in the primary endpoint (a composite of fatal and nonfatal myocardial infarction, stroke, and other cardiovascular deaths); however, the incidence of diabetes was lower in the captopril group than in the conventional group (RR, 0.86; $p = 0.039$) *(86,87)*. In the Heart Outcomes Prevention Evaluation (HOPE) Study, a placebo-controlled trial, use of the ACE inhibitor ramipril was associated with a reduction in the development of diabetes (RR, 0.66; 95% CI, 0.51–0.85) *(88)*. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, the risk of developing diabetes was 13.0/1000 patient-years in the group randomized to begin therapy with the angiotensin receptor blocker losartan and 17.4/1000 patient-year in the atenolol-based group (RR, 0.75; 95% CI, 0.63–0.88) *(89)*. In a substudy to the LIFE trial, losartan was shown to have more favorable effects than atenolol on insulin resistance *(90)*.

In ALLHAT, the risk of developing diabetes during 4 yr of follow-up was also associated with treatment. The group treated with chlorthalidone had the highest 4-yr incidence (11.6%) followed by amlodipine (9.8%, $p = 0.04$ versus chlorthalidone) and lisinopril (8.1%, $p < 0.001$ versus chlorthalidone) *(63)*. In ASCOT-BPLA, the incidence of developing diabetes was less on the amlodipine-based regimen than on the atenolol-based regimen (RR, 0.70; 95% CI, 0.63–0.78) *(66)*. In aggregate, these results support the contention that ACE inhibitors, angiotensin receptor blockers and calcium channel blockers may provide some protection against the development of diabetes. The failure of this protection against diabetes to translate into superiority over diuretics in trials of CVD outcomes may relate to the duration of the CVD outcomes trials having been too brief to observe the long-term effects of diabetes prevention on risk of CVD. However, in the 14.3 yr follow up of the SHEP participants, there was no increase in cardiovascular or all-cause mortality for those who had developed incident "diabetes" during the trial in the chlorthalidone group, whereas those in the placebo group with incident diabetes had significantly higher mortality than those who did not develop diabetes or those with incident diabetes in the chlorthalidone group *(91)*. In addition, the 2–6 mg/dL lower glucose seen in trials with ACE inhibitors or angiotensin receptor blockers compared with other drugs would be predicted to have a rather small effect on CVD outcomes. In the ACCORD trial, for example, a Hgb A1c difference of 1.5%, similar to a fasting glucose difference of approx 55–60 mg/dl, is estimated to be needed to produce a 15% difference in CVD events in 10,000 participants over 5 yr. This is ten times the glucose difference observed between antihypertensive drugs. Therefore, it is not surprising, in studies like ALLHAT and SHEP, there were no CVD outcome effects of differences in glucose or diabetes incidence. Furthermore, other differences between the antihypertensive agents in mechanisms of cardiac protection may be operative.

## PRACTICAL ASPECTS OF BLOOD PRESSURE CONTROL IN DIABETES

A summary of treatment recommendations is provided in Table 4.

The literature reviewed above supports the conclusion that high blood pressure is a major risk factor for macro- and micro-vascular disease in patients with diabetes. Indeed, as a consequence of the higher baseline risk in patients with diabetes and the manner in which the presence of high blood pressure multiplies that already elevated risk, the absolute excess risk of adverse outcomes related to high blood pressure is much greater in patients with diabetes than in those without diabetes. Owing to the aforementioned increased risk for macro-and micro-vascular disease, treatment of high blood pressure is a high priority in patients with diabetes. As recommended by JNC7,

**Table 4**
**Practical recommendations for the treatment of high blood pressure in type 2 diabetes mellitus**

| *Category* | *Recommendation* | *Evidence Grade* |
|---|---|---|
| Treatment Goals | SBP should be controlled to < 150 mm Hg | 1A |
| | SBP should be controlled to < 140 mm Hg | 1B |
| | SBP should be controlled to < 130 mm Hg consistent with JNC 7 | 2C |
| | DBP should be controlled to < 80 mm Hg consistent with JNC 7 | 1A |
| Drug Therapy | Thiazide-type diuretics should be used as first line therapy for uncomplicated high blood pressure in patients with diabetes. | 1A |
| | ACE inhibitors and calcium channel blockers should be used as second line agents or as alternative first line agents for patients who do not tolerate diuretics. | 1A |
| | Angiotensin receptor blockers (ARB) may be used for patients who do not tolerate ACE inhibitors (except when angioedema is the reason for intolerance). | 1A |
| | Many, if not most, patients with diabetes will need 3 medications to reach goal (especially SBP < 130 mm Hg). | 1A |
| | Initial therapy with a combination of a diuretic and an ACE inhibitor (or ARB) would be reasonable for most patients with diabetes and high blood pressure. | Expert opinion |
| | When 3 medications are needed, combination therapy with a diuretic, ACE inhibitor (or ARB) and calcium channel blocker would be reasonable. | Expert opinion |
| | Beta adrenergic receptor blockers, alpha blockers, reserpine, hydralazine, and centrally acting sympatholytics are reasonable alternatives as third line agents. | Expert opinion |
| | Choice of blood pressure lowering medications should be influenced by other indications for use of specific agents. | Varies by agent and indication. |

it may be reasonable to treat patients with diabetes at lower blood pressure levels and to aim for lower blood pressure goals; however, strong evidence from clinical trials is currently lacking to support this approach.

In the interim, control of SBP to less than 130 mm Hg and DBP to less than 80 mm Hg is recommended in JNC 7 *(16)*. This level of control can be challenging to achieve and usually requires combination antihypertensive therapy. However, identification of an evidence based approach to combination therapy is difficult, because most of the randomized trials have applied constraints on the regimens that have impaired their subsequent clinical applicability. In ALLHAT, approx 60% of participants were controlled to SBP < 140; however, the ALLHAT protocol prohibited, or at least strongly discouraged, any combined use of diuretics, ACE inhibitors and calcium channel blockers. The second and third line agents approved by the protocol included atenolol, clonidine, reserpine, and hydralazine *(63)*. In the subgroup of participants with diabetes, the mean SBP ranged from 135 to 137 mm Hg across the treatment groups despite the use of 2 medications on average *(64)*. In ASCOT, 53% of participants reached both their systolic and diastolic blood-pressure targets, but only 32% of patients with diabetes reached their intensive targets of SBP < 130 and DBP < 80 mm Hg. ASCOT also limited the use of therapies to amlodipine plus perindopril versus atenolol plus bendroflumethiazide *(66)*. In UKPDS, just over 60% of participants in the more intensively treated group received 2 or more medications, and 29% received 3 or more medications to achieve a mean blood pressure of 144/82 mm Hg; however, the protocol discouraged the combined use of ACE inhibitors and beta-blockers *(54)*. No study has examined the effectiveness of triple drug therapy with a diuretic, ACE inhibitor (or angiotensin receptor blocker) and calcium channel blocker either in patients with or without diabetes.

Nevertheless, it is clear from the ALLHAT, ASCOT and UKPDS experiences that the majority of patients with diabetes and high blood pressure will need 3 or more medications to achieve SBP < 130 mm Hg *(54,63,66)*. Because most patients will need multiple drugs to achieve good blood pressure control, it may be reasonable to begin therapy with a combination medication that includes a diuretic and an ACE inhibitor. In those instances in which a single agent may be sufficient to achieve good blood pressure control, cost and efficacy considerations support

the use of diuretics. ACE inhibitors may be reasonable alternatives, especially in patients with microalbuminuria or macroproteinuria.

Angiotensin receptor blockers are reasonable substitutes for ACE inhibitors when the latter are not tolerated owing to cough; however, angioedema has been reported in patients on angiotensin receptor blockers, so other alternative therapies may be preferable when patients experience angioedema with an ACE inhibitor. When a third medication is needed, a calcium channel blocker may be a reasonable choice. Beta-blockers, reserpine, or alpha blockers may be useful when more than 3 medications are needed or when patients do not tolerate medications from other classes. The choice of blood pressure lowering medications should also be influenced by other specific indications (e.g., beta-blockers in patients with compensated heart failure or known CAD).

In the ACCORD Trial, an intensive blood pressure lowering strategy was developed by one of the clinical sites to assist them in pursuing the target SBP < 120 mm Hg. That strategy, which was influenced by the formulary available in ACCORD, recommends initiation with benazapril/hydrochlorothiazide as step 1, switch to diuretic plus benazapril/amlodipine for step 2, switch to metoprolol/hydrochlorothiazide plus benazapril/amlodipine for step 3, and addition of reserpine when needed for step 4. An alternative strategy was developed for participants who do not tolerate ACE inhibitors. Both candesartan with (and without) hydrochlorothiazide and valsartan with (and without) hydrochlorothiazide are available in the ACCORD formulary, so the use of either of these combination medications with amlodipine and metoprolol would provide presumably similar blood pressure lowering effectiveness to the step 3 regimen described above. This alternative strategy requires participants to use a larger number of pills per day, possibly decreasing adherence and increasing cost. Strategies that minimize the number of different pills taken per day may help enhance adherence and limit the cost to patients, at least in terms of co-pays. Another strategy to consider in clinical practice, which is also available in ACCORD, is to change the thiazide-type diuretic from hydrochlorothiazide to chlorthalidone, because chlorthalidone 12.5–25 mg/d appears to have more antihypertensive efficacy than hydrochlorothiazide 25–50 mg/d, especially throughout the 24-h dosing period *(92)*.

## PREVENTION OF HIGH BLOOD PRESSURE AND DIABETES AS APPROACHES TO CONTROL COMPLICATIONS

Prevention of diabetes and high blood pressure may be the most effective long-term approaches to preventing high-blood-pressure-related events in patients with diabetes. The Finnish Diabetes Study *(93)* and the Diabetes Prevention Program *(94)* provide strong evidence that lifestyle change approaches to promote healthy diet and increased physical activity can reduce the risk of diabetes by more than 50%. The Dietary Approaches to Stop Hypertension Trial provides strong evidence that similar lifestyle changes can reduce blood pressure levels *(95)*. In the long-term, it may be much more effective to promote lifestyle change approaches than to attempt to medicate the over 60 million Americans with hypertension *(2)* and the over 20 million Americans with diabetes *(96)*. Although there are currently no long-term studies indicating that prevention of diabetes and hypertension is sustainable or that short-term prevention translates into reduced morbidity or mortality attributable to either disease, trends in blood pressure and diabetes reflect the importance of societal influences on diet, physical activity and adiposity in populations. Greater attention should be placed on understanding and improving these influences on health. Until efforts to prevent high blood pressure and diabetes are more effective, efforts to improve the quality of medical care will remain crucial to the control of diabetes- and high-blood-pressure-related complications.

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# 17 Lipoproteins in Diabetes: Risk and Opportunity

*John R. Guyton*

***Contents***



**Summary**

Lipoproteins play a central role in atherosclerosis, the leading cause of death in patients with diabetes mellitus. Diabetic dyslipidemia largely results from hepatic overproduction of very low density lipoproteins, stimulated by a high flux of nonesterified fatty acids from adipose tissue to the liver. The dyslipidemia is characterized by high plasma triglyceride, low levels of high density lipoproteins, and small, dense low density lipoproteins —all of which contribute to the atherogenic state in diabetes.

Atherosclerosis is accelerated by multiple other factors in diabetes in addition to lipoprotein abnormalities. For example, the accumulation of advanced glycosylation endproducts in arterial tissue may produce chronic inflammatory responses. Even in this milieu, epidemiologic data and clinical trials suggest that intensive treatment targeting lipoproteins can markedly reduce diabetic cardiovascular risk. Recognizing that average or "normal" lipoprotein levels predict adverse outcomes in diabetic patients, the health care provider should use dietary, lifestyle, and pharmacologic treatment to make lipoprotein parameters considerably better than average.

## INTRODUCTION

Atherosclerosis is the most common serious complication of diabetes mellitus. An estimated 60–75% of people with diabetes will die of an atherosclerotic event such as myocardial infarction or stroke. Cardiovascular events are 2–4 times more common in diabetic versus nondiabetic people *(1,2)*.

Because lipoproteins play a central role in atherogenesis, an important question to be addressed in this chapter is the manner and the degree to which altered lipoproteins—diabetic dyslipidemia—may contribute to the elevated risk of diabetes. However, an equally important issue is the degree to which lipoproteins contribute to atherosclerotic cardiovascular events among all persons in the developed, industrialized world. Regardless of diabetic status, atherosclerotic risk is 3–10 times higher than in undeveloped societies *(3–5)*. In recent clinical trials, low density lipoprotein (LDL) cholesterol levels typical of undeveloped societies have been achieved, and marked risk reduction has been the rule. Lipoproteins in diabetes do carry special *risk,* but even more they offer

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*opportunity* to reduce diabetes-associated risk. Reduction of cardiovascular events in diabetes may be gained by treating lipoproteins to targets that are considerably better than average level in the developed world.

With these goals in mind, this chapter will review fundamental concepts of lipoprotein metabolism and atherogenesis, address the special features of dyslipidemia in diabetes, and then emphasize aspects of evidence-based practical treatment.

## FUNDAMENTALS OF LIPOPROTEIN METABOLISM

### *General Properties and Physical Chemistry of Lipids*

Phospholipids form the essential bilayer structure of cell membranes and participate in many specialized lipid functions. Cholesterol, which is present in most membranes of the cell, increases the "stiffness" or viscosity of the phospholipid bilayer and makes it less permeable to water and small organic molecules *(6)*. Membranes do not self-assemble with exactly the proper ratios of cholesterol to phospholipids for ideal function; instead, multiple gene products function in overlapping systems to actively maintain membrane homeostasis. There is considerable evidence that these systems all fail in the lipid-rich core of atherosclerotic plaques, and vascular cells may die there from overaccumulation of cholesterol that disrupts critical membrane functions *(7)*.

Fatty acids supply most of the fuel used by skeletal muscle, heart muscle, and many other tissues. The transport or storage of large quantities of fatty acids is made more efficient by esterification to form triglyceride. Likewise, cholesterol is esterified to form cholesteryl ester for transport or storage. These lipid esters are insoluble in water, leading to their efficient nonaqueous packing in oily droplets in cells or in the oily core of lipoproteins. Moreover, esterification reactions also represent cellular defense mechanisms, preventing the overaccumulation of cholesterol or fatty acids that could disrupt membrane structure and function *(8)*. Cholesteryl ester and triglyceride are nontoxic owing to their sequestration in oily droplets and their minimal presence in cell membranes *(9)*.

### *Lipoproteins and Apolipoproteins*

For circulatory transport, cholesterol, cholesteryl ester, triglyceride, and phospholipid are packaged together with specific proteins (apolipoproteins) in spherical pseudomicellar structures, the plasma lipoproteins (Fig. 1). The surface monolayer of amphiphilic phospholipid molecules provides an aqueous-oily interface that allows the particle to dissolve in water. Plasma lipoproteins are separable into distinct classes on the basis of their equilibrium

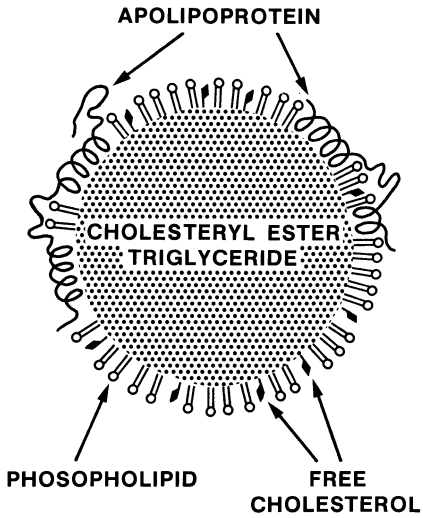


**Fig. 1.** Lipoprotein structure. Plasma lipoproteins are generally spherical particles containing a hydrophobic core composed of triglyceride and cholesteryl ester and having a surface coat whose primary component is a phospholipid monolayer. Interspersed in the phospholipid coat are free cholesterol and apolipoproteins. Reproduced with permission from Via DP, Guyton JR, Gotto AM Jr: Atherosclerosis: lipoprotein metabolism, in Vascular Medicine, 2nd ed., eds. Loscalzo J, Creager MA, Dzau VJ, Little Brown and Co., Boston, 1996.

**Table 1**
**Four major classes of lipoproteins**

| | *Chylomicrons* | *Very low density lipoproteins (VLDL)* | *Low density lipoproteins* | *High density lipoproteins* |
|---|---|---|---|---|
| Major core lipid | Triglyceride | Triglyceride | Cholesteryl ester | Cholesteryl ester |
| Apolipoproteins | B-48, Cs, E, A-I, A-II | B-100, Cs, E | B-100 | A-I, A-II, Cs, E |
| Density (gm/mL) | <0.93 | 0.93–1.006 | 1.006–1.063 | 1.063–1.210 |
| Diameter (nm) | 75–1200 | 30–80 | 18–25 | 5–12 |
| Origin | Intestine | Liver | From VLDL, via peripheral/hepatic processing | Liver, intestine |

From references *(150–153)*

densities by ultracentrifugation (Table 1). The density of lipoproteins is directly related to surface-to-volume ratio, and thus to the inverse of radius. Large lipoproteins (chylomicrons and very low density lipoproteins [VLDL]) have abundant core lipid ester (less dense) relative to surface phospholipid and protein (more dense), and thus are the most buoyant lipoproteins. The converse is true for high density lipoproteins (HDL), which are the smallest circulating pseudomicellar structures and have a high content of surface phospholipid/protein relative to core lipid ester.

The apolipoproteins (Table 2) play essential roles in the determination of lipoprotein structure and the regulation of lipid transport. Most apolipoproteins contain one or more peptide sequences that form alpha-helical regions, hydrophobic amino acids facing one side of the helix and hydrophilic amino acids facing the side 180° opposite. The amphiphilic character of these helical domains accounts for the binding of the protein in the lipoprotein surface monolayer (Fig. 1) *(10)*.

Apolipoprotein A-I (apoA-I) and apolipoprotein B (apoB) can be regarded as essential structural apolipoproteins because virtually all plasma lipoproteins contain either apoA-I or apoB or, in the case of chylomicrons, both. ApoA-I and apoA-II are the major apolipoproteins of HDL. All lipoproteins of density less than 1.063 g/mL (chylomicrons, VLDL, IDL, and LDL) contain apoB. ApoB-48 is synthesized only in the intestine and is found

**Table 2**
**Major apolipoproteins**

| *Apolipoprotein* | *Molecular weight* | *Distribution* | *Function* |
|---|---|---|---|
| A-I | 28,000 | HDL, chylomicrons | structural role in HDL; participates in ABC-A1-mediated cholesterol efflux; activates lecithin-cholesterol acyltransferase |
| A-II | 17,000 | HDL, chylomicrons | structural role in HDL |
| B-48 | 264,000 | Chylomicrons | structural role in intestine-derived lipoproteins |
| B-100 | 550,000 | LDL, IDL, VLDL, chylomicrons | structural role; ligand for LDL receptor binding |
| C-II | 9,100 | VLDL, IDL, HDL, chylomicrons | activates lipoprotein lipase |
| C-III | 8,750 | VLDL, IDL, HDL, chylomicrons | inhibits lipoprotein lipase |
| E | 34,000 | IDL, VLDL, chylomicrons, HDL | ligand for LDL receptor binding of IDL; promotes hepatic uptake of chylomicron remnants |
| [a] | 400,000–700,000 | Lipoprotein [a], chylomicrons | unknown |

From references *(151–153)*

only in chylomicrons and their remnant particles, whereas apoB-100 is produced almost entirely in the liver. A single apoB-100 molecule is bound noncovalently to each VLDL particle in the liver and remains with the particle through its metabolism to IDL and LDL. Because of its huge size (550 kDa) and hydrophobicity, the binding of apoB to lipoprotein particles is irreversible, lasting until cellular uptake and lysosomal hydrolysis of the particles *(11)*.

The regulatory functions of apoA-I, apoB-100, apoC-II, apoC-III, and apoE are now well established, as described in Table 2. These apolipoproteins function by mediating lipoprotein binding to cell surface receptors or by acting as cofactors or inhibitors for enzymes involved in lipoprotein lipid metabolism *(12)*.

## *Fatty Acid and Triglyceride Metabolism*

Fatty acids are the major fuel for muscles in the body and are also important precursors of lipid and nonlipid synthetic pathways. Fatty acids supply 2-carbon units via acetyl-CoA for synthetic additions in metabolism—e.g., the synthesis of cholesterol. However, fatty acids cannot supply the 3-carbon intermediates that are necessary for anaerobic energy production, nor can fatty acids serve as precursors for gluconeogenesis *(13)*.

Intestinal absorption of fat depends first upon hydrolysis of triglyceride to fatty acids and monoglycerides by pancreatic lipase. This process is aided by bile salts, which assist lipolysis and absorption by forming micelles in the intestinal lumen. Inside the intestinal mucosal cells, fatty acids are re-esterified to glycerol and assembled in the triglyceride core of chylomicrons. The chylomicrons are secreted into intestinal lymph and enter the blood circulation via the thoracic duct.

Figure 2 shows pathways for lipoprotein transport from the central organs, gut, and liver to peripheral tissues. Chylomicrons carry triglyceride synthesized in the gut. VLDL are secreted by the liver and carry triglycerides of hepatic origin. Both of these triglyceride-rich lipoproteins are metabolized by lipoprotein lipase in the peripheral circulation. The enzyme hydrolyzes triglyceride, but not cholesteryl ester; the fatty acids thus liberated diffuse into capillary endothelial membranes and subsequently into the tissue parenchyma. As a result of lipoprotein lipase action, the triglyceride-rich lipoprotein shrinks in size. The resulting chylomicron remnant is rapidly taken up by hepatocytes. The VLDL remnant (also called intermediate density lipoprotein, or IDL) may either undergo hepatic uptake or further processing at the hepatocyte surface by hepatic lipase to produce an LDL particle. Genetic absence of lipoprotein lipase or its apolipoprotein cofactor, apoC-II, leads to massive plasma triglyceride accumulation in chylomicrons. Severe insulin deficiency can downregulate lipoprotein lipase activity with the same result (discussed later).

Metabolism of hepatic fatty acid and triglyceride is strongly influenced by plasma levels of free fatty acids and insulin. Plasma free fatty acids are taken up avidly by the liver, where they are incorporated into triglyceride and tend to augment the secretion of VLDL. Obesity is the most common condition associated with elevated plasma free fatty acids and consequently with high plasma triglyceride. Insulin deficiency and alcohol ingestion also increase VLDL secretion and heighten plasma triglyceride levels, at least partly through elevation of plasma free fatty acids *(14,15)*.

## *Cholesterol Metabolism*

### Dietary and Endogenous Cholesterol

Cholesterol absorption in the intestine is unregulated and incomplete, amounting to 30 to 60% of the cholesterol entering the intestine. Dietary cholesterol may amount to 200–400 mg daily, whereas biliary cholesterol makes a larger contribution to intestinal contents, about 900 mg daily. Cholesterol is solubilized in the intestinal lumen by bile acids, forming mixed micelles *(16)*. Plant sterols and stanols can reduce plasma cholesterol levels by competitively inhibiting cholesterol incorporation into the micelles *(17)*. Intestinal cholesterol enters the absorptive cells by facilitated transport involving the recently discovered Niemann-Pick C1-like-1 (NPC1L1) protein. In the cells, cholesterol undergoes esterification. Cholesteryl ester, along with much larger amounts of triglyceride, is incorporated into chylomicrons and secreted into intestinal lymph *(16)*.

Only one third or less of cholesterol added to total body stores comes from diet. Two thirds or more is synthesized. In cholesterol synthesis, 3 molecules of acetyl-CoA are joined to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), which is then reduced to make mevalonic acid. Six molecules of mevalonic acid then pass through

multiple intermediate steps to form farnesyl pyrophosphate, squalene, and finally cholesterol *(18)*. A major rate-limiting enzyme in cholesterol synthesis is HMG-CoA reductase, the activity of which is under feedback control by the level of cellular cholesterol. The key transcriptional regulators are sterol regulatory element-binding proteins (SREBPs), which are retained in the endoplasmic reticulum under conditions of cholesterol loading, but are transferred to the Golgi complex, cleaved, and subsequently translocated to the nucleus in cholesterol-depleted cells *(19)*.

### Reverse Cholesterol Transport and HDL

Recently it was recognized that peripheral tissue cells make most of the cholesterol in the body *(149)*. In general, cholesterol cannot be degraded or metabolized by most cells, and any excess must be transported to the liver for disposal. This is traditionally called "reverse cholesterol transport," although we now understand that it quantitatively exceeds the movement of cholesterol via LDL from liver to peripheral cells. Mechanisms of reverse cholesterol transport are complex and not yet completely understood *(20–22)*. The adenosine triphosphate-binding cassette A1 (ABC-A1) cell membrane transporter on peripheral tissue cells is a binding site for lipid-poor apoA-I/phospholipid complexes, and cellular cholesterol along with additional phospholipid is transferred to the complexes, forming disc-shaped "nascent HDL." The plasma enzyme lecithin-cholesterol acyltransferase (LCAT) associates with the nascent HDL particle and esterifies its cholesterol, thereby forming an oily interior within the particle and transforming it into spherical mature HDL. Cholesteryl ester in HDL has 2 major routes of delivery to the liver. The first involves binding of HDL to the scavenger receptor B1 (SR-B1) on hepatocytes, direct transfer of cholesteryl ester from the HDL particle into the hepatocyte, and subsequent release of the HDL particle. The HDL is then able to return to the peripheral tissues to pick up more cholesterol. The second major way of delivering cholesterol from HDL to the liver involves cholesteryl ester transfer protein, which mediates the bidirectional exchange of cholesteryl ester and triglyceride between HDL and the larger lipoproteins, VLDL and LDL. The larger, apoB-containing lipoproteins ultimately deliver cholesteryl ester to the liver via receptor-mediated pinocytic uptake.

Mature spherical HDL are heterogeneous with regard to size, density, and composition. HDL2 is larger and more buoyant; HDL3 is smaller and denser. HDL3 is converted to HDL2 by the transfer of surface components from triglyceride-rich lipoproteins as a consequence of lipoprotein lipase action *(23)*. Hepatic lipase converts HDL2 back to HDL3. Most of the clinical factors that affect HDL cholesterol levels primarily affect HDL2, including heredity, hormones, obesity, and exercise *(24,25)*.

### Hepatic Cholesterol Metabolism and LDL

The liver is the destination for reverse cholesterol transport and is the source for cholesterol delivered to body tissues via VLDL and LDL. Triglyceride-rich VLDLs are transformed by lipolysis in circulating plasma to intermediate density lipoproteins and subsequently to LDL (Fig. 2). Peripheral tissue cells take up LDL particles by receptor-mediated endocytosis. Because all cells of the body can synthesize cholesterol (and most do), the physiologic function of LDL is actually unknown today. The liver itself displays LDL receptors, and about two thirds of total LDL catabolism occurs in the liver. Maneuvers that decrease plasma LDL concentration often work by increasing hepatic LDL receptor activity and LDL catabolism, rather than decreasing LDL production *(26)*.

Liver cholesterol is derived from 4 sources: uptake of chylomicron remnants bearing cholesterol absorbed in the intestine, de novo synthesis in the liver, uptake of plasma lipoproteins including LDL, and transfer of cholesteryl ester from HDL via the SR-B1 receptor. Hepatic cholesterol balance requires that input must be matched with output. Total output of cholesterol from the liver is comprised of secretion in VLDL into the circulation, biliary secretion of cholesterol, and conversion into bile acids with subsequent biliary secretion. Bile acids undergo an enterohepatic circulation by virtue of efficient reabsorption (about 95%) in the terminal ileum. Fecal loss of cholesterol, bile acids, and their colonic bacterial degradation products constitutes the major route of cholesterol elimination from the body *(16)*. The enterohepatic circulation of bile acids can be interrupted by oral administration of ion-exchange polymers, such as cholestyramine, colestipol, and colesevelam that bind bile acid anions, or by surgical bypass of the terminal ileum. When this occurs, the conversion of cholesterol to bile acids and the synthesis of cholesterol in the liver both increase markedly. The net effect is that hepatic cholesterol decreases, LDL receptors are upregulated, and plasma LDL levels fall *(16,26)*.

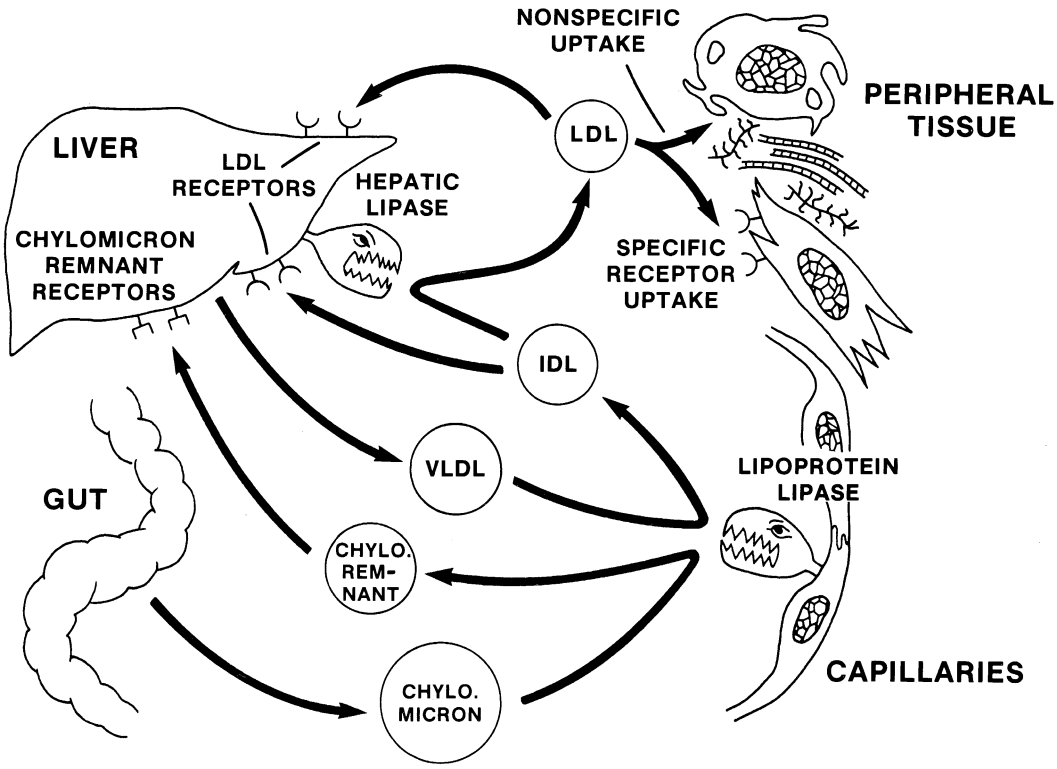


**Fig. 2.** Pathways for apoB-containing lipoproteins. Chylomicrons enter the circulation after being secreted into lymph by intestinal mucosal cells. Lipoprotein lipase, located on the luminal surface of capillary endothelium, hydrolyzes triglyceride in chylomicrons, allowing free fatty acids to diffuse into parenchymal tissue. The chylomicron remnants thus produced are rapidly taken up by hepatocytes. VLDL is secreted by the liver and is acted upon similarly by lipoprotein lipase. IDL, which represents remnant particles from VLDL, may be taken up via hepatocyte LDL receptors or may be further metabolized with the help of hepatic lipase to form LDL. There are three possible fates for circulating LDL: 1) uptake via hepatic LDL receptors, 2) uptake by genetically identical LDL receptors located on peripheral cells, and 3) nonspecific uptake by binding to extracellular tissue components or unregulated receptors on scavenger cells such as macrophages.

### Cellular LDL Uptake and Lipid Metabolism

The LDL receptor is a transmembrane glycoprotein localized in clathrin-coated pits on the cell surface. Coated pits invaginate and deliver LDL to lysosomes, where its protein and lipid components are hydrolyzed. The resulting increase in cellular cholesterol leads to retention of SREBPs in the endoplasmic reticulum rather than transport to the nucleus, and thus to transcriptional suppression of HMG-CoA reductase, activation of acyl-CoA:cholesterol acyltransferase (ACAT), and downregulation of cell surface LDL receptors *(19)*. ACAT catalyzes intracellular cholesterol esterification and sequestration in cytoplasmic oily droplets, which may protect the cell from the deleterious effects of excess unesterified cholesterol *(8)*.

### Lipoprotein(a)

Lipoprotein(a), sometimes abbreviated Lp(a), resembles an LDL particle to which a large glycoprotein, apolipoprotein(a), is joined via disulfide linkage to apoB. This is usually a minor lipoprotein carrying only a very small amount of plasma cholesterol. LDL cholesterol, as it is usually measured by precipitation techniques, includes lipoprotein(a) cholesterol. In a minority of persons, lipoprotein(a) can be relatively abundant and even account for most of plasma "LDL." The physiologic role of lipoprotein(a) remains uncertain. Its importance rests in strong positive associations with coronary and other atherosclerotic disease. Individuals of subSaharan African ancestry have higher lipoprotein(a) levels on average than whites and Asians, but the atherogenic associations of lipoprotein(a) are unclear among Africans and African-Americans *(27)*. Related to its evolutionary derivation from the plasminogen gene, the apolipoprotein(a) gene product appears to inhibit physiologic thrombolysis. It is

therefore prothrombotic as well as atherogenic *(28)*. Lipoprotein(a) plasma levels are not affected by statins or other lipid-lowering medications, except that niacin in doses of 2,000–3,000 mg/d can reduce lipoprotein(a) by 25% *(29)*. Lipoprotein(a) alterations have been described in diabetes and insulin resistance, but they are relatively minor *(30)*. The key role of lipoprotein(a) measurement is to disclose a genetic and largely unmodifiable influence on cardiovascular risk.

## LIPOPROTEINS AND ATHEROSCLEROSIS

### *High Intimal LDL*

In the arterial intima, LDL is both abundant and stagnant. The concentration of LDL in the arterial intima is approximately equal to its concentration in blood plasma *(31,32)*. This contrasts sharply with the concentrations of LDL in other connective tissues, estimated at one-tenth of plasma concentration based on measurements in lymph *(33)*. Thus the arterial intima is uniquely exposed to very high levels of LDL in contact with connective tissue matrix molecules—collagen, elastin, proteoglycans. This remarkable circumstance is owing to the lack of lymphatic vessels in the arterial intima (high hydrostatic pressure in the intima may preclude lymphatic ingrowth). Lymphatic vessels act as sumps to drain away excess macromolecular species accumulating in the extracellular space, and this critical tissue function is lacking in the arterial intima. Furthermore, the residence time of LDL in the intima may be weeks to months, because of limited permeability of the endothelium and of the tunica media *(34)*. High levels and long residence of LDL maximize the opportunity for enzymatic, oxidative, and other processes to disrupt the integrity of individual LDL particles, exposing hydrophobic or other sites that mediate aggregation, fusion, and matrix-binding of the particles, as well as foam cell formation *(35)*. The arterial intima has been described as a cesspool for LDL *(36)*.

### *Accumulation of lipid – lesion progression*

*Fatty streaks* are early atherosclerotic lesions that appear in the teenage years in the coronaries and the aorta (Fig. 3). These lesions neither thicken the intima nor predispose to thrombosis, and thus are important only as precursors to more advanced lesions. Histologically fatty streaks contain lipid-filled macrophages and lesser numbers of lipid-bearing smooth muscle cells. The macrophages are derived from circulating monocytes that migrate from the blood across arterial endothelium - an effect mediated by cellular adhesion molecules upregulated in the setting of hypercholesterolemia, immune processes, smoking, or hypertension.

Beginning at about age 20, raised lesions, or *fibrous plaques*, begin to appear in the proximal coronaries, in the iliac arteries, and in the carotids—and later in other large arteries. The thickened intima in these lesions is owing to proliferation of smooth muscle cells and macrophages and to synthesis of large amounts of collagen and other fibrous tissue proteins. The majority of plaques possess a lipid-rich, hypocellular or acellular core region. However, the initiation of the lipid-rich core appears to occur earlier, having been identified in flat aortic lesions—i.e., fatty streaks *(7,37)*. This finding suggests that fibrous plaques may develop from pre-existing fatty streaks (Fig. 3).

As the fibrous plaque grows and begins to impinge upon the arterial lumen, the entire artery undergoes a compensatory enlargement *(38)*. The mechanism is likely to be endothelial-dependent regulation of arterial lumen diameter governed by blood velocity and wall shear rate *(39)*. Eventually, however, the compensatory enlargement fails, perhaps when the collagenous lesion extends almost all the way around the circumference of the artery, leaving little normal wall to respond to blood shear. Abnormalities in endothelial-dependent relaxation of arteries have been described in diabetes, and multiple mechanisms appear to link this phenomenon with the increase in atherogenic events *(40)*.

The most dangerous part of the atherosclerotic lesion is the lipid-rich core. After its initiation deep in the intima, this site of marked lipid infiltration and cellular apoptosis gradually enlarges and progressively erodes the lesion fibrous cap. When the fibrous cap finally ruptures, blood rapidly dissects into the core, and the core contents, notably containing large amounts of thrombogenic tissue factor, erupt into the arterial lumen, rapidly leading to partial or complete thrombosis of the artery *(7,41)*.

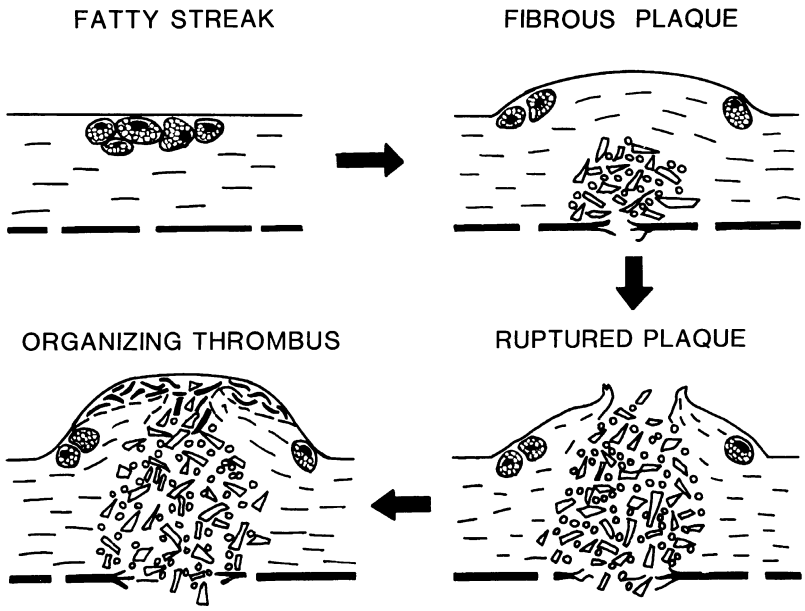


**Fig. 3.** Lesion development. The fatty streak is a flat lesion composed of foam cells. The fibrous plaques is a raised lesion that usually, but not always, contains a cholesterol-rich, a cellular core. Rupture of a fibrous plaque occurs after the expanding core weakens the support of the endothelial surface to the breaking point. The luminal thrombus resulting from plaque rupture is organized by ingrowth and proliferation of smooth muscle cells, leading to rapid, episodic growth of advanced lesions.

### *Relationship to Inflammation*

An early indication of the inflammatory nature of atherosclerosis was the discovery that complement is activated in the atherosclerotic lipid-rich core. Either crystalline cholesterol monohydrate or cholesterol-rich phospholipid vesicles may activate the complement system, generating terminal C5b-9 complexes. The complement C3b receptor and iC3b receptor, as well as the complement regulatory glycoprotein, decay accelerating factor (DAF), were identified in human lesions, but not in normal arterial wall *(42)*.

Cytokines generally function locally to influence cellular gene expression and behavior. Platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) have been implicated in the growth response of arterial smooth muscle in models of arterial injury *(43,44)*. The transforming growth factor-β(TGFβ) family of 3 closely related polypeptides enhances the production of collagen by smooth muscle cells, but suppresses macrophage inflammatory responses *(45,46)*. A cell surface protein on T lymphocytes in lesions, called CD40 ligand (also known as CD154) may exert critical pro-inflammatory effects in atherosclerosis *(47)*. On the other hand, interferon-γ(IFNγ) secreted by T lymphocytes appears to modulate the atherosclerotic process in a complex and at least partly beneficial manner *(48)*. The inflammatory cytokines interleukin-1 (IL-1β) and tumor necrosis factor-α(TNFα) have multiple effects—shifting endothelial anticoagulant/procoagulant balance toward procoagulant effect, enhancing growth factor expression in smooth muscle cells, and increasing expression of matrix metalloproteinases *(49)*.

The NFκB family of transcription factors integrates diverse stimuli into an array of inflammatory responses. This system responds to ligation of receptors for TNFα or IL-1β, or the cellular receptor for advanced glycosylation endproducts, in a pathway that includes increased intracellular levels of reactive oxygen species. Genes with NFκB response elements include those encoding macrophage chemotactic peptide-1, tissue factor, several adhesion molecules including vascular cell adhesion molecule-1, and early response genes involved in cell proliferation *(50)*.

Atherosclerosis is clearly a form of chronic inflammation in the arterial wall. Epidemiologic studies have linked cardiovascular events with circulating inflammatory markers, of which the most predictive is C-reactive protein. When measured by a high-sensitivity assay, C-reactive protein adds significantly to cardiovascular risk prediction even after taking other known risk factors into account *(51)*.

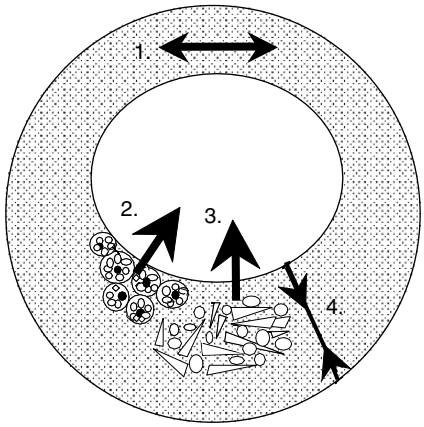


**Fig. 4.** Four ways for risk to improve in an atherosclerotic lesion. 1) Dilation of a normal segment of the arterial wall. 2) Regression of foam cells in the lesion cap or shoulder. 3) Removal of lipid from the core. () Regression of fibrous tissue. Of these potential processes, 4 is likely the most difficult to achieve. Even without regression of fibrous tissue, a vulnerable plaque can be stabilized.

### *Advanced Glycosylation End Products*

The discovery of a cellular receptor for advanced glycosylation end products (AGEs and their receptor, RAGE) was pivotal for understanding 2 key questions about diabetic complications. First, it offered an explanation of the hyperglycemic threshold effect for diabetic complications. If AGEs are responsible for the damage, then the development of complications may depend on a race between AGE formation owing to hyperglycemia and their removal via receptors on scavenger cells. If removal mechanisms lose the race (owing to elevated ambient glucose levels), then long-term accumulation of AGEs in the arterial wall will occur. Ironically, the initial receptor, RAGE, may not participate in removal or detoxification of AGEs, but a number of other cellular receptors are candidate garbage collectors *(52)*.

Secondly, RAGE explains how AGE accumulation may lead to chronic inflammatory responses. Ligand-engagement of RAGE on vascular wall cells causes generation of reactive oxygen species, activation of NFκB, and expression of a range of proinflammatory molecules *(52)*. In tissues such as arterial intima, AGEs may constitute the "memory" of a number of years of postprandial hyperglycemia that leads to poorly reversible atherosclerotic inflammation, even at the outset of clinically evident diabetes *(53)*.

### *Stabilization of the Vulnerable Plaque*

Atherosclerotic regression is often conceptualized as a decrease in atherosclerotic intimal thickening that results in decreased stenosis. Such regression may occur, but a more readily achievable goal of lipid management is the stabilization of vulnerable lesions prone to rupture and thrombosis (Fig. 4). For example, hypercholesterolemia can interfere with normal function of endothelium, and decreases in LDL cholesterol can normalize endothelial-dependent relaxation, possibly improving the resistance to thrombosis as well *(54)*. Lipid lowering can also cause relatively rapid disappearance of macrophage foam cells from lesions. Because macrophages in a lesion directly correlate with propensity to rupture *(55)*, the elimination of macrophages may effectively stabilize the lesion fibrous cap, prevent rupture, and forestall atherothrombotic events.

## LIPOPROTEINS IN THE DIABETIC PATIENT

### *Diabetic Dyslipidemia*

The dyslipidemia of diabetes is marked by increased plasma concentrations of triglyceride-rich lipoproteins, decreased concentrations of HDL, and a shift in the sizes of both LDL and HDL toward smaller, denser particles. Insulin-resistant individuals often have the same dyslipidemia before onset of diabetes.

A primary abnormality leading to diabetic dyslipidemia is an increased flux of fatty acids from adipose tissue to liver (Fig. 4). Insulin resistance, insulin deficiency, or both lead to a failure of suppression of hormone sensitive

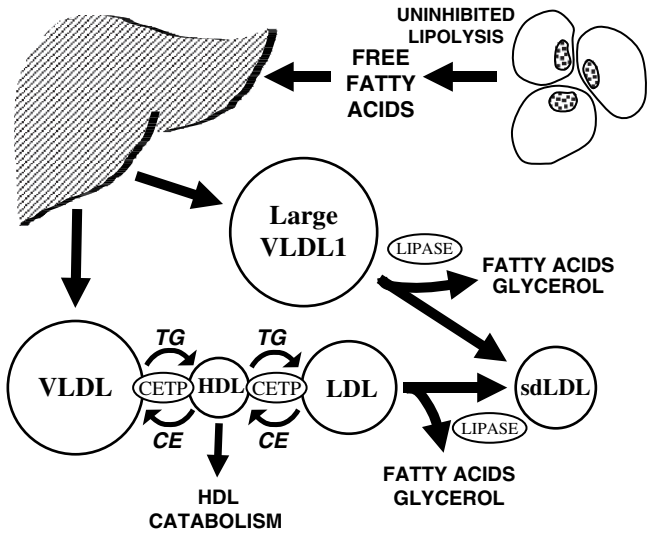


**Fig. 5.** Genesis of diabetic dyslipidemia. The lack of inhibition of lipolysis in adipocytes, owing to insulin deficiency and/or insulin resistance, leads to increased flux of free (nonesterified) fatty acids to the liver. The liver then secretes more VLDL and, in particular, the large VLDL subfraction called VLDL1. Cholesteryl ester transfer protein (CETP) mediates exchange of triglyceride and cholesteryl ester between VLDL and HDL, resulting in triglyceride-enriched HDL. These HDL particles, especially after interaction with hepatic lipase, are unstable and tend to shed apolipoprotein A-I with the net result of HDL catabolism. CETP also mediates triglyceride enrichment of LDL, and the subsequent action of hepatic lipase reduces LDL size, producing small dense LDL (sdLDL). Small dense LDL may also be produced by the lipoprotein lipase/hepatic lipase cascade acting on large VLDL1.

lipase in adipocytes, promoting the release of nonesterified fatty acids into plasma. The chief response of the liver is to package and export the fatty acids as triglyceride in VLDL, raising the levels of VLDL in plasma. The fatty acids from VLDL triglyceride largely end up cycling back to adipose tissue via the action of lipoprotein lipase. However, lipoprotein lipase activity is reduced in the diabetic or insulin resistant state, and plasma levels of VLDL triglyceride are thereby accentuated *(56,57)*.

The shift toward smaller LDL size is the result of 2 major pathophysiologic mechanisms (Fig. 5). First, most of the VLDL in diabetic or insulin resistant patients contains much more triglyceride per particle than average VLDL. This subpopulation of large VLDL (VLDL1) is destined to undergo extensive lipolytic processing to become small dense LDL *(161)*. Second, cholesterol ester transfer protein (CETP) mediates the exchange of core neutral lipids—triglyceride and cholesteryl ester—among lipoprotein particles. When VLDL are abundant, then the triglyceride exchanged from VLDL will tend to replace cholesterol ester in both LDL and HDL. The triglyceride-enriched LDL and HDL are subject to processing by hepatic lipase, leading to a net loss of core neutral lipid. Both LDL and HDL attain smaller sizes by this mechanism *(58)*.

When HDL are reduced in size by the concerted action of CETP and hepatic lipase, some of the apolipoprotein A-I occupying the HDL surface must be shed. The released, lipid-poor apolipoprotein A-I, as a small peptide, passes through the glomerular filter in the kidney, and is hydrolyzed in the tubular cells. This mechanism contributes to the well-known inverse relationship between plasma triglyceride and HDL cholesterol levels *(56)*.

Epidemiologic data suggest that small dense LDL are more atherogenic than large buoyant LDL. Mechanisms proposed for atherogenicity include lower levels of antioxidants per particle, increased permeation of arterial endothelium, and prolonged particle residence in plasma with accumulation of lipid peroxides *(57)*.

### *Fasting Chylomicronemia*

Ordinarily chylomicrons interact very efficiently with peripheral lipoprotein lipase, so that dietary fat is rapidly cleared from the blood. Under conditions of marked insulin deficiency, however, lipoprotein lipase activity greatly diminishes. Chylomicrons may then be found in blood 24 h a day (i.e., fasting chylomicronemia), and continued ingestion of fat will cause enormous accumulation of chylomicrons in circulating blood. The organ most commonly affected is the exocrine pancreas. Local intravascular activation of pancreatic lipase and generation

of fatty acids forming soaps (fatty acid anions) may be the critical step. By detergent action on pancreatic cell membranes, additional digestive enzymes may be released, leading to a vicious cycle of damage.

The risk of pancreatitis becomes substantial when plasma triglyceride levels exceed 2000 mg/dl. However, baseline fasting triglyceride levels of 500–800 mg/dL can set the stage for rapid chylomicron accumulation with continued ingestion of fat or alcohol. Therefore, dietary and pharmacologic treatment of hypertriglyceridemia above 500-800 mg/dl is recommended for prevention of pancreatitis. In the presence of chylomicron-associated symptoms (with or without serum amylase or lipase elevation) or triglyceride levels above 2,000 mg/dL, dietary treatment should emphasize strict avoidance of dietary fat. At lower triglyceride levels, dietary treatment is problematic (discussed later in this chapter), because high carbohydrate intake can help to sustain hypertriglyceridemia. If the cause of fasting chylomicronemia is uncontrolled diabetes mellitus, insulin treatment is mandatory and will resolve the chylomicronemia over several days. However, even tight glycemic control rarely causes complete normalization of plasma triglyceride *(14,59)*.

Other manifestations of the chylomicronemia syndrome with triglyceride levels above 2000 mg/dl include eruptive xanthomas—triglyceride-containing papules that often appear in crops on the extremities or trunk. Microcirculatory clogging by the large triglyceride-rich particles (up to a micron in diameter) can result in dyspnea, aggravation of coronary ischemia, or memory/psychiatric disturbances. Lipemia retinalis generally signifies even higher triglyceride levels, above 3,000–4,000 mg/dL *(14,59)*.

## LIPOPROTEIN TREATMENT TARGETS

### *Goals for LDLC*

People with type 2 diabetes often have 20% or higher risk of myocardial infarction or coronary death over 10 yr, a rate similar to that of nondiabetic patients with clinical coronary heart disease. Therefore, the Adult Treatment Panel III (ATP-III) guidelines of the U.S. National Cholesterol Education Program (NCEP) consider type 2 diabetes mellitus to be risk equivalent with established coronary artery disease. This equivalency holds true for most ethnic populations including South Asians. In East Asian groups such as Japanese and Chinese, however, cardiovascular risk of diabetic patients is likely less than that of patients with established coronary disease, because of the low overall risk for atherosclerotic disease in these populations *(60)*. Estimation of primary risk in type 1 diabetes is less certain because of lack of data and a younger age range. Nevertheless, a target for LDL cholesterol below 100 mg/dL is recommended by both the NCEP and the American Diabetes Association for all persons with diabetes. A compelling additional reason for aggressive LDL treatment is the poor prognosis of diabetic patients in the acute setting of myocardial infarction and in long-term CHD followup *(60)*. Because 100 mg/dL represents approximately the 15th percentile in the US for LDL cholesterol in both men and women over the age of 50, the vast majority of older adults with diabetes will need LDL-lowering treatment *(60)*.

In patients with especially high risk, such as diabetic patients who have already manifested clinical atherosclerotic disease, the goal of LDLC <100 mg/dL might not be low enough. For these and other patients with very high risk, an optional LDLC goal of less than 70 mg/dL was suggested by the NCEP Adult Treatment Panel in a 2004 paper discussing the implications of recent clinical trials. The NCEP interim report also suggested that lipid-lowering drug therapy generally should attempt to reduce LDLC by at least 30–40% *(61)*. The clinical research trial that most specifically addressed a lower LDLC goal was the Treating to New Targets (TNT) Study *(162)*. Patients with clinically evident CAD were entered into the study if their LDLC was <130 mg/dL while taking atorvastatin 10 mg daily. They were randomized to either 10 mg or 80 mg of atorvastatin daily, achieving mean LDLC of 101 mg/dL (2.6 mmol/L) or 77 mg/dL (2.0 mmol/L), respectively. Patients receiving the higher dose of atorvastatin had 22% fewer major cardiovascular events over a period of 5 yr ($p < 0.001$). The results support the idea of a lower LDLC treatment goal in very high risk patients.

The focus on LDL as a treatment target is strongly supported by large randomized clinical trials, most of which used statins to reduce LDL (see below under drug treatment). Further support for LDL as a treatment target comes from the United Kingdom Prospective Diabetes Study (UKPDS), in which LDL cholesterol emerged as the strongest modifiable risk factor in an epidemiologic analysis that also included HDL cholesterol, triglyceride, hemoglobin A1c, fasting glucose, blood pressure, and smoking *(62)*.

### *HDL Cholesterol*

The NCEP guidelines recognize HDL cholesterol < 40 mg/dL as a major cardiovascular risk factor. Raising low levels of HDL is recommended, but a specific goal has not been set. The American Diabetes Association (ADA) standards of care list HDL cholesterol levels >40 in men and >50 in women as desirable *(63,64)*.

The Veterans Administration HDL Intervention Trial (VA-HIT) found that gemfibrozil significantly reduced major cardiovascular events by 24% in men with prior coronary heart disease and low HDL cholesterol. Although gemfibrozil both raises HDL and lowers triglyceride, only the increased HDL cholesterol levels correlated significantly with event reduction in a multivariate analysis *(65)*. Among 627 diabetic men in VA-HIT, gemfibrozil significantly reduced major cardiovascular events by 32% *(66)*. Niacin, a drug that raises HDL better than gemfibrozil, was shown to reduce myocardial infarction and cerebrovascular events in the Coronary Drug Project (CDP) *(67)*. At the time HDL cholesterol was minimally recognized as a risk factor, and measurements of HDL were not performed.

These and other studies suggest that HDL could be regarded as an additional treatment target in patients with and without diabetes. The suggestion is bolstered by UKPDS results showing that HDL cholesterol contributes independently to cardiovascular risk in diabetes *(62)*. Moreover, the pathophysiologic understanding of the role of HDL in reverse cholesterol transport and other mechanisms of protection from atherosclerosis has advanced greatly in recent years.

The selection of a specific treatment target for HDL cholesterol—e.g., >40 mg/dL—is hampered by the wide scatter of baseline HDL levels in the population. It has been suggested that the total/HDL cholesterol ratio provides a better target, which depends mostly on HDL after the primary LDL target has been addressed *(68)*. Canadian guidelines give a total/HDL cholesterol ratio target of <4 for diabetic patients over the age of 30 *(69)*.

### *Triglyceride and Non-HDL Cholesterol*

In the era before the recognition of HDL as a risk factor, Albrink suggested that triglyceride was equally important with cholesterol in determining atherosclerotic risk in diabetes *(70)*. In UKPDS, the adjusted hazard ratio of 1.7 from lowest to highest triglyceride tertile was almost as high as the ratio of 2.2 for LDL cholesterol tertiles. However, HDL is a strong inverse covariate of triglyceride. After accounting for the effect of HDL cholesterol, triglyceride did not contribute independently to cardiovascular risk in UKPDS *(62)*.

Triglyceride as a treatment target is not supported by the results of VA-HIT, because neither baseline nor on-treatment levels of triglycerides correlated with event rates *(65)*. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, triglyceride was reduced almost 30%, but the primary endpoint of major coronary events was not reduced significantly *(71)*.

The NCEP and the ADA agree that a triglyceride level <150 mg/dL is desirable *(63,72)*. NCEP does not designate 150 mg/dL or any other level as a specific goal, but instead names nonHDL cholesterol as a secondary treatment target (after LDL cholesterol) in patients with triglyceride over 200 mg/dL. Non-HDLC goals are 30 mg/dL higher than the corresponding LDLC goals for each category of risk. Thus the non-HDLC goal is <130 mg/dL in diabetes. As mentioned earlier, triglyceride levels above 500–800 mg/dL need consideration of dietary and drug treatment to prevent pancreatitis.

### *Apolipoprotein B and LDL Subfraction Analysis*

A recent international conference has called for measurement of apolipoprotein B to supplement and eventually replace LDL and non-HDL cholesterol in cardiovascular prevention guidelines *(73)*. The suggestion is based mainly on epidemiologic evidence that the total number of atherogenic lipoprotein particles is the most important determinant of lesion progression and atherosclerotic events. Every atherogenic particle contains one molecule of apolipoprotein B; therefore, apolipoprotein B mass is proportional to particle number. Apart from epidemiology, however, the pathophysiologic meaning of particle number is much less clear, because the strongest pathologic evidence describes the role of *cholesterol* in lesion evolution, not *apolipoprotein B*. Even so, it is quite possible that cholesterol delivered to the arterial wall in smaller, more numerous particles, and perhaps postprandially in remnant lipoproteins (which also contain apolipoprotein B), may produce a greater imbalance of lipids in the lesion core than cholesterol in large, buoyant LDL.

Commercially available assays for LDL subfractions, particle size, and particle number have been available for several years *(74–76)*. These assays potentially provide new targets for lifestyle and drug treatment, but consensus guidelines do not yet provide goals.

The NCEP guidelines recognize other emerging risk factors, which include lipoprotein(a), C-reactive protein, and evidence of subclinical atherosclerosis. New imaging techniques for subclinical atherosclerosis may eventually blur the distinction between primary and secondary prevention. The techniques include enhanced computed tomographic scanning for coronary calcium quantitation and B-mode ultrasound for carotid intima-media thickness quantitation *(77)*. Where available, either technique might be appropriately used in cases where cardiovascular risk is uncertain or perhaps thought to be higher than Framingham estimates, such as patients with exceptionally strong family history. Nevertheless, all of the emerging risk factors lack conclusive evidence of treatment benefit and should only be used as modulators of clinical risk assessment.

## DIETARY AND LIFESTYLE TREATMENT OF DYSLIPIDEMIA

Dietary treatment of lipoproteins is applicable to all persons with diabetes, and drug treatment will be recommended for most. Even in patients requiring lipid-modifying drugs, dietary compliance remains important, especially for hypertriglyceridemia.

### *Dietary Considerations for Hypercholesterolemia*

Saturated fat is the most important dietary factor altering hepatic cholesterol metabolism to raise plasma LDL concentration. It has considerably greater effect on plasma LDL than does variation of dietary cholesterol within the usual range *(72)*. The impact of dietary change can be gauged as follows: The average US diet contains 11% of calories as saturated fat *(78)*. Consider a change from this diet with typical initial cholesterol intake of 325 mg/d to the saturated fat (<7%) and cholesterol (<200 mg) guidelines of the Therapeutic Lifestyle Change diet recommended by NCEP and ADA. An average 14 mg/dL reduction of plasma cholesterol is predicted by the well-validated equation of Keys and Parlin *(79)*. This could give 10–15% reduction of cardiovascular risk *(80)*. Thus diet is important, but the total LDL cholesterol reductions often will be insufficient to meet treatment goals in diabetes.

Transunsaturated fatty acids comprise 2.5–3.5% of all calories consumed in the US. Most of it comes from the commercial hydrogenation of vegetable oils, which extends the shelf life of snack foods and lowers the cost of deep fat frying. A minor quantity of trans fat is produced by bacterial action in the ruminant stomach, thus appearing in milk fat and meat from cattle and sheep. Dietary trans fat gives higher LDL cholesterol and lower HDL cholesterol compared to naturally prevalent *cis*-unsaturated fat *(81)*. In short-term trials, trans fat increased serum levels of the inflammatory markers, interleukin-6 and C-reactive protein. An epidemiologic meta-analysis has suggested that the incidence of coronary heart disease in a population increases a remarkable 23% when trans fat contributes 2% of total dietary calories *(82)*. Trans fat should be eliminated from or minimized in the diet of people with diabetes.

Three kinds of "functional foods"—phytosterol and phytostanol esters, viscous fiber, and soy protein—merit consideration for LDL lowering. Plant sterols competitively inhibit intestinal absorption of cholesterol, but poor solubility and miscibility characteristics make them ineffective in practice. Miettinen and colleagues recognized that fatty acid esterification of the plant sterols could make them miscible with dietary fat and enhance the lowering of plasma cholesterol. Margarines containing plant sterol/stanol esters can lower LDL cholesterol as much as 10–14%.*(17)* Viscous fiber was previously known as soluble fiber (after years of waiting, it failed to dissolve, and the name was changed). It reduces LDL cholesterol up to 10% via intestinal or hepatic effects. It is found in substantial amounts in oats, legumes, other vegetables and fruits, but not in wheat or corn *(83,84)*. Soy protein reduces LDL cholesterol through a mechanism that is not yet clear.

Jenkins and colleagues studied a near-vegan "dietary portfolio" of cholesterol-lowering foods, which included plant sterol/stanol ester margarine and the bulk of calories coming from viscous fiber-rich foods and soy protein. In comparison with a near-vegan diet based on whole wheat cereals and low fat dairy products, the dietary portfolio gave 29% versus 8% reduction of LDL cholesterol and 28% versus 10% reduction of C-reactive protein,

respectively *(84)*. The effects of functional foods may partly underlie the similar LDL cholesterol lowering seen previously in the dietary and lifestyle treatment of heart disease by Ornish and colleagues *(85)*.

Literally hundreds of other dietary supplements have been reported to lower cholesterol on the basis of small clinical trials of uncertain validity. Among these, garlic is ineffective or only mildly effective, policosanol is questionable, and cinnamon is very preliminary.(86-88)

To facilitate recognition of dietary/lifestyle effects on lipoproteins, the clinician should be aware of the effects of intervening clinical events. For example, 10–30% temporary reductions of both LDL and HDL occur following significant tissue injury including myocardial infarction and surgical intervention *(89)*. Short-term weight loss of just a few pounds over 3–6 wk can also give substantial reduction of both LDL and HDL, whereas long-term maintenance of lower weight raises HDL and gives much less reduction of LDL *(90)*.

### *Dietary and Lifestyle Considerations for Hypertriglyceridemia*

Recommendations for dietary management of hypertriglyceridemia in diabetes are controversial and may be changing. We will outline 2 areas of consensus and then highlight the controversy.

First, high dietary intakes of high glycemic carbohydrates clearly can raise plasma triglyceride *(91)*. In persons who excessively consume regular soda, presweetened tea, fruit juice, and/or sports drinks, stopping these beverages sometimes eliminates hypertriglyceridemia. The Nurses' Health Study found that dietary glycemic load was strongly associated with plasma triglyceride and also increased the risk of new onset diabetes *(92)*. In a 6-wk randomized, multi-center trial, a high carbohydrate diet resulted in significantly higher plasma triglyceride as well as loss of glycemic control, compared to a diet high in monounsaturated fat *(93)*.

Second, very low carbohydrate diets reduce plasma triglyceride levels more effectively than low fat diets over short periods of time, up to 6 mo *(94,95)*. In an early metabolic ward study, a diet containing only 7–15% of calories as carbohydrate and 60–65% as fat was an effective treatment for severe hypertriglyceridemia while total caloric intake and body weight were maintained *(96)*. Questions arise, however, about whether very low carbohydrate diets can be sustained and whether they are safe and effective over the long term *(97,98)*. It would seem dangerous, for example, to institute a very low carbohydrate, high fat diet suddenly in a patient with severe hypertriglyceridemia, because the limited lipoprotein lipase activity available for clearing plasma triglyceride may be overwhelmed by dietary fat. Pancreatitis could result, as described in a recent case report *(99)*. Thus very low carbohydrate diets need to be applied very carefully and need more study before they can be generally recommended for hypertriglyceridemia in diabetes.

Weight loss is generally effective in reducing plasma triglyceride *(94,98)*. Moreover, weight loss improves insulin resistance, glycemic control, and inflammation parameters such as C-reactive protein, making weight loss a key issue in diabetes treatment regardless of lipids. Some of the leading investigators in obesity research have pointed to the success of low fat diets for losing weight and maintaining reduced weight. Low fat, weight-reducing diets were employed in 2 long-term trials that showed success in prevention of type 2 diabetes in subjects at high risk *(100,101)*. Low fat diets can better incorporate high fiber and whole grain foods with suggested health benefits *(102)*.

Bray has noted that either a fat-restricted or a carbohydrate-restricted diet could help to limit caloric intake, because of "sensory-specific satiety" *(103)*. The concept, described by Rolls and colleagues, is that appetite is separate for carbohydrate-rich versus fat-rich foods. By limiting food choices to one category (along with some source of protein), we fill up quicker, and we do not compensate by overeating one to make up for the lack of the other *(104)*. The converse, as Bray put it, is that a meaty, fat-rich meal still leaves room for a sweet dessert, and thus we overeat *(103)*. Does this mean that a diet with balanced macronutrients could be the *least* advantageous for weight loss? A recent trial of 4 diverse diets suggested that any diet, including a balanced diet, can be successful if applied conscientiously *(98)*.

Is it possible to make sense of the seemingly disparate data and to define the best diet for diabetic dyslipidemia? A call for more effectiveness/quality research as well as efficacy research (randomized trials) should be heeded *(105)*. Individualized diet prescription may be best, perhaps even consecutive dietary trials to discover what suits a patient best by criteria of weight loss and metabolic improvement.

## DRUG TREATMENT OF DYSLIPIDEMIA

Effective drug regimens for dyslipidemia utilize, singly or in combination, drugs from 6 groups—inhibitors of hydroxymethylglutaryl coenzyme A reductase (statins), cholesterol absorption inhibitor (ezetimibe), niacin, fibric acid derivatives, bile acid sequestrants, and fish oil. Each of these drug classes, except for ezetimibe, has been shown to prevent clinical cardiovascular events in randomized clinical trials conducted largely in nondiabetic subjects.

### *Statins*

Statins lower LDLC by 20–60%, lower triglyceride by 15–35%, and raise HDLC modestly (2–14%). No other drugs have better proven safety or efficacy in reducing cardiovascular events *(106)*.

In early randomized trials of statin therapy, relative risk reductions for cardiovascular events were about the same among small numbers of patients with diabetes, compared with nondiabetic patients *(107,108)*. The first randomized trial to include a large number of diabetic patients was the Heart Protection Study with 5,963 diabetic subjects, of whom half had pre-existing occlusive arterial disease. Simvastatin 40 mg daily was found to reduce major cardiovascular events by 25–33% (the higher figure taking into account noncompliance and crossover treatment). Pretreatment LDLC levels were below 116 mg/dL (3.0 mmol/L) in 2,426 diabetic participants, and a 27% reduction of cardiovascular events was found in this group. Risk reductions were found among all prespecified subgroups and for various manifestations of atherosclerotic disease, including myocardial infarction, coronary death, strokes, and revascularizations *(110)*. The Collaborative Atorvastatin Diabetes Study (CARDS) included 2,838 subjects, all with diabetes and with no previous documented history of cardiovascular disease. Participants were randomly assigned to atorvastatin 10 mg daily or placebo. Average baseline LDLC was 117 mg/dL (3.03 mmol/L), and LDLC was reduced 40% in the treatment group. Major cardiovascular events were reduced 37% in the treatment group. Again the findings extended to all classes of events and all subgroups examined *(109)*.

In an early randomized trial, it appeared that statin treatment might reduce the incidence of new onset diabetes *(111)*. However, this finding was probably caused by chance alone, because the statistical significance was marginal, and subsequent large trials did not reproduce the finding *(110,112)*.

Statins competitively block the synthesis of mevalonic acid in cellular metabolism. Although mevalonic acid leads to several other metabolites besides cholesterol, statins do not ordinarily interfere with crucial cellular functions, or with the synthesis of steroid and sex hormones that use cholesterol as a precursor. Hepatic transaminase levels are monitored after initiation of statin therapy or dosage increase, but instances of hepatic failure or fibrosis are almost unknown *(113)*. In 0.1–0.8% of patients, depending on predisposing characteristics, statin monotherapy can lead to myopathy with serum creatine kinase (CK) elevation >10 times the upper limit of normal, rarely progressing to rhabdomyolysis. Dose, age, hypothyroidism, female gender, chronic kidney disease, and east Asian ethnic background are some predisposing factors. Myopathy and sometimes rhabdomyolysis can result from an interaction of statins with cyclosporine or gemfibrozil. Some but not all statins also interact with inhibitors of the cytochrome p450 3A4 system such as erythromycin, clarithromycin, and azole antifungals *(114)*.

A dilemma arises when the patient complains of myalgia and CK levels are less than 5 times the upper limit of normal. CK levels in this low range are usually constitutive or exercise-induced, and rarely correlate with symptoms. Nevertheless, symptoms of myalgia or weakness demand clinical judgment, because muscle damage can occur without CK elevation *(115)*. If symptoms require it, the statin dose may be reduced 4-fold, sometimes giving only half a tablet every other day. The dose reduction may on occasion be coupled with a switch to a different statin, or nonstatin therapy may be added or substituted entirely for the statin.

### *Ezetimibe*

Ezetimibe is the first member of a new pharmacologic class that inhibits cholesterol absorption by intestinal mucosa. Ordinarily the intestine is exposed to 200–400 mg dietary cholesterol and 900 mg biliary cholesterol daily, of which 30–60% may be absorbed. After ingestion, ezetimibe is concentrated in intestinal mucosal brush border, where it appears to bind to a membrane sterol transporter. Ezetimibe at 10 mg daily gives 18–19% LDLC lowering. When ezetimibe is added to an existing statin regimen, LDLC is reduced 20–25% from the poststatin baseline. Side effects of ezetimibe have been minimal and not significantly different from placebo *(116)*.

### *Fibrates*

Fibric acid derivatives, or fibrates, approved for use in the US include gemfibrozil, fenofibrate, and a rarely used older drug, clofibrate. The fibrates perform best at lowering triglyceride levels; reductions of 40–55% can be expected in hypertriglyceridemic patients. HDLC increases of 6–20% can occur. Fenofibrate reduces LDL cholesterol moderately in normotriglyceridemic patients. Fibrates are agonists for the peroxisome proliferator-activated receptor alpha (PPAR-alpha) transcription factor that regulates hepatic lipid metabolism. Triglyceride lowering may be accomplished largely by downregulating hepatic synthesis of apoC-III, which inhibits the action of lipoprotein lipase on triglyceride-rich lipoproteins. PPAR-alpha is also involved in the regulation of inflammatory pathways, and suppression of inflammation has been observed in experimental models *(117)*.

The evidence for cardiovascular risk reduction by fibrates is mixed, with moderate benefits shown by various drugs in the setting of low HDLC, high triglyceride, metabolic syndrome, and/or diabetes. Clofibrate, an older drug, is rarely used today because of increased all-cause mortality seen in a randomized trial *(118)*. In a primary prevention trial targeting hypercholesterolemic men in the 1980s, gemfibrozil reduced nonfatal myocardial infarctions. There were few coronary deaths in the study, and no difference afforded by gemfibrozil, but noncardiovascular deaths trended higher in the gemfibrozil versus placebo group *(119,120)*. Gemfibrozil significantly reduced cardiovascular events by 24% in the Veterans Administration HDL Intervention Trial (VA-HIT), a secondary prevention trial of men with low HDLC *(65)*. A large subgroup with diabetes showed a trend toward greater risk reduction at 32% *(66)*. In another secondary prevention trial, bezafibrate, a drug available in Europe, gave a nonsignificant 7% reduction of major coronary events *(121)*. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study enrolled 9,795 diabetic patients, of whom 2,131 had previous clinical cardiovascular disease. The primary outcome, occurrence of coronary death or nonfatal myocardial infarction, trended 11% lower in the fenofibrate versus placebo group ($p = 0.16$). This was mirrored by an 11% reduction of total cardiovascular events including revascularizations, and this was statistically significant owing to greater numbers ($p = 0.035$). The benefit of fenofibrate in FIELD was diluted by the fact that more placebo-treated patients started statin therapy as the trial proceeded. A prespecified analysis taking this fact into account suggested that fenofibrate might reduce cardiovascular risk by 14–19%. However, the benefit in FIELD was confined to reductions of nonfatal cardiovascular events; cardiovascular and noncardiovascular mortality both trended higher in patients taking fenofibrate (11% and 10%, respectively). Other concerns about fenofibrate use included a failure of the subgroup with previous cardiovascular disease to benefit at all and increased incidences of pancreatitis (0.8% versus 0.5% placebo) and venous thromboembolism (1.1% versus 0.7%). On the other hand, fenofibrate-treated patients had less need for laser treatment of retinopathy and less albuminuria progression. Overall, FIELD suggested that fenofibrate has modest efficacy for cardiovascular prevention *(71)*.

In patients with isolated low HDLC or hypertriglyceridemia, not requiring or not tolerating statins, the evidence supports the use of gemfibrozil over fenofibrate. However, for combination therapy with statins, fenofibrate has a marked safety advantage over gemfibrozil (see the following). A major NIH-funded study, currently in progress, is examining the role of fenofibrate addition to statin therapy in diabetes (www.accordtrial.org).

Because both gemfibrozil and fenofibrate are cleared from the circulation largely by the kidney; doses should be decreased in patients with renal insufficiency. Side effects shared by these drugs include dyspepsia, hypersensitivity rash, hepatic transaminase elevations, increased warfarin effect, and increased lithogenicity of bile. Fenofibrate can increase serum creatinine, perhaps by augmenting creatinine production in muscle *(163)*. Fenofibrate rarely causes dermal photosensitivity *(122)*.

### *Niacin*

Niacin, also known as nicotinic acid, is a form of vitamin B3. Lipid-lowering doses can be 50–100 times the vitamin dose. Niacinamide (nicotinamide) also acts as a vitamin, but has no lipid-lowering effect. Nicotinic acid binds to a newly described G-protein coupled receptor on adipocytes, resulting in inhibition of lipolysis and decreased plasma free fatty acid levels *(123)*. It also acts in the liver to decrease the production of VLDL and decrease catabolism of HDL and apoA-I *(124)*. Niacin is the most effective pharmacologic agent for raising HDLC; daily doses of 1,000 to 2,000 mg raise HDLC by 12–25% *(125)*. Doses in the range of 1,500–3,000 mg/d reduce triglyceride, LDLC, and lipoprotein(a) levels.

Niacin has a remarkably consistent record of benefit in clinical trials assessing mortality, morbidity, and cardiovascular anatomic endpoints. The Coronary Drug Project (CDP), a 5-yr randomized placebo-controlled trial begun in the late 1960s, showed a 26% reduction in nonfatal myocardial infarction and a 24% reduction in cerebrovascular events with niacin treatment *(67)*. Follow up of the CDP population 9 yr after the end of the trial revealed an absolute 6.2% reduction in total mortality in the niacin-treated group. An even more striking reduction of ischemic heart disease mortality occurred in the Stockholm Ischemic Heart Disease Study, which utilized combination treatment with clofibrate and pentaeritrityl tetranicotinate *(126)*. Three studies reported in 1990 that examined immediate-release niacin in combination therapy all showed beneficial effects on cardiovascular anatomic endpoints *(127–129)*.

More recently, the HDL Atherosclerosis Treatment Study showed reversal of angiographically determined coronary atherosclerosis using a statin-niacin combination regimen, and statistically significant 70% reduction of clinical cardiovascular events *(130)*. In a placebo-controlled study of 143 subjects with coronary heart disease, combination therapy with immediate-release niacin, gemfibrozil, and cholestyramine provided regression of coronary angiographic disease, versus progression in the control group *(131)*. Only 9 of the treated subjects experienced a cardiovascular event versus 19 of the controls ($p = 0.04$).

Niacin causes insulin resistance, but quantitative and clinically applicable data are sparse *(132–134)*. Insulin secretory responsiveness does not decline. With long-term administration of extended-release niacin at 2,000 mg/d, fasting glucose levels rise 4–5% *(135)*. Despite the presumption of insulin resistance, in the 5-yr Coronary Drug Project, niacin treatment was as effective in reducing cardiovascular endpoints in patients with hyperglycemia as it was in patients with normoglycemia *(136)*. Niacin-related insulin resistance hypothetically might be expected to increase the incidence of new onset diabetes mellitus. However, in the same 5-yr placebo-controlled study, no significant increases were found for new prescriptions for insulin, new prescriptions for oral antidiabetic agents, or instances of dipstick-positive glycosuria *(67)*.

Two recent studies showed that niacin can be used safely and effectively in patients with type 2 diabetes. Extended-release niacin was administered at dosages of 1,000 and 1,500 mg/d in a placebo-controlled study of 148 type 2 diabetes patients *(137)*. Fasting blood glucose demonstrated a slight increase early with niacin treatment but returned to baseline by week 16. Hemoglobin A1c did not change significantly in the placebo or 1000 mg niacin groups, but increased from 7.2% to 7.5% ($p = 0.048$) in the 1,500 mg/d group. Four patients discontinued the study owing to inadequate glucose control. Similar statistically significant but small changes in glycemic parameters were reported with immediate-release niacin prescribed at 1,500 mg twice daily in a 1-yr study of diabetic patients with peripheral arterial disease *(138)*. In this study, the fraction of patients requiring insulin for diabetes increased 13% in the niacin-treated group, compared to 4% in the placebo group (not significant, $p = 0.09$).

Niacin commonly causes flushing, usually experienced as "prickly heat" on the head and shoulders. Flushing tends to disappear with repetitive and consistent dosing over days to months. When prescribing niacin, it is very important to describe flushing to the patient before it occurs. Immediate-release niacin can be given 2–4 times per day preferably in the middle of meals, beginning with 100–125 mg and increasing over weeks to months to 1,000–2,000 mg total daily dose, or sometimes higher. Sustained-released niacin is more prone to hepatotoxicity, and the total dose should be limited to 2,000–2,250 mg daily. An extended-release prescription form of niacin (Niaspan), given once daily at bedtime, has well documented hepatic safety in doses up to 2,000 mg. Inositol hexanicotinate, called "no-flush" niacin," has not been shown to affect lipids. Aspirin 325 mg or another anti-inflammatory drug can be taken 30 min before niacin ingestion to reduce flushing. Chewing an 81 mg aspirin tablet might shorten the duration and decrease the severity of flushing once it occurs. Side effects of niacin also include dyspepsia, transaminase elevations, atrial fibrillation, peptic ulcer, gout, skin dryness, hypotension (with a severe flush), and visual disturbances (macular edema, rare with doses under 3,000 mg/d) *(139)*.

### *Bile Acid Sequestrants*

Bile acid sequestrants (BAS) include cholestyramine and colestipol, which are therapeutically very similar, and colesevelam, which has better tolerability. These nonabsorbed polymers bind bile acids in the small intestine, preventing their reabsorption in the terminal ileum. By depleting hepatic cholesterol used to synthesize bile acid,

the sequestrants reduce LDL cholesterol 10–30%. Triglyceride levels tend to increase, and severe hypertriglyceridemia is a relative contraindication to the use of BAS. Because BAS are not absorbed into the bloodstream, they have excellent theoretical and practical safety, sufficient to recommend them for reducing LDLC in pediatric cases and in women of childbearing potential. The major side effects of cholestyramine and colestipol are constipation (15% of cases) and abdominal bloating. Drug absorption may be inhibited, particularly warfarin, vitamin K (in warfarin-treated patients), digoxin, diuretics, and thyroxine. Colesevelam has much better gastrointestinal tolerability and minimal drug interactions *(140)*. Interestingly, cholestyramine was shown to improve glycemic control modestly in type 2 diabetic subjects *(141)*, an effect that might be shared by other bile acid sequestrants.

### *Omega-3 Fatty Acids*

Nutritional intake of omega-3 fatty acids has been associated with 20–30% reduction of cardiovascular mortality and 30–50% reduction of rates of sudden death. Animal experiments have suggested resistance to ventricular fibrillation. A current recommendation is that coronary patients ingest 1 g of omega-3 fatty acids daily from marine sources, either from fatty fish or from capsules. It is reasonable to substitute omega-3 fatty acids from terrestrial sources – flaxseed, walnuts, and canola oil—if fish oil is not tolerated *(142)*.

Fish oil can also be used for triglyceride lowering. Marine, but not terrestrial, omega-3 fatty acids lower plasma triglyceride by as much as 30–45%. High daily doses are required (e.g., 3.4 to 5 grams omega-3 fatty acids, or 15 typical capsules, or 1 tablespoon of liquid fish oil). A prescription formulation of concentrated omega-3 ethyl esters effectively lowers triglyceride at a dose of four 1-gram capsules daily *(143)*.

### *Combination Drug Therapy*

Because LDLC <100 mg/dl is the goal in patients with atherosclerotic disease, combinations of the medications listed above are often used. Statin with ezetimibe is now the most commonly used combination because of tolerability. If gemfibrozil is used in combination with a statin, up to 4% of patients may experience myopathy, unless the statin dose is kept at or near the usual starting dose. Niacin and fenofibrate are generally safe to use in combination with statins, although a few case reports of rhabdomyolysis have appeared *(144,145)*. Ezetimibe, bile acid sequestrants, and fish oil can be added to statin therapy or to niacin and fibrates without an increased risk of myopathy or other synergistic adverse effects *(146)*.

## TREATMENT OF LOW HDL

The powerful inverse correlation between HDL and cardiovascular events suggests that raising HDLC or apolipoprotein A-I might reduce macrovascular risk in diabetes as much as lowering LDL. Emerging data supports this concept, as reviewed earlier, but it should not be regarded as proven *(136,147)*. The potential impact of HDL-raising may be underestimated by clinicians, because small changes in HDL concentration are associated with relatively large changes in risk. Data from 4 large prospective studies suggested that a 1 mg/dL increase in HDL may give 2–3% reduction of cardiovascular risk *(148)*.

Success in raising HDL levels is sometimes considered difficult to achieve, but combinations of nonpharmacologic and pharmacologic treatment can be effective in most patients. Both saturated and *cis*-unsaturated fat (poly- and monounsaturated fat, but not trans fat) raise HDL cholesterol levels modestly when replacing dietary carbohydrate *(81)*. This and other measures are reviewed in Table 3. It is not unusual to see a 50% increase in HDLC in a patient who makes a dietary change, takes up running, adds alcohol intake, and begins niacin treatment. Because of its adverse individual and social effects, alcohol should be recommended seldom, cautiously, and with profound respect for personal and family values. Large randomized trials are currently underway testing the effects of adding niacin to statins for reducing cardiovascular events.

**Table 3**
**Interventions to raise HDL cholesterol**

| *Intervention* | *Dose or quantity* | *% HDLC change* | *% ApoA-I change* |
|---|---|---|---|
| Nonpharmacologic | | | |
| Long-term weight loss | 20 pounds | 5–10% | – |
| Increased dietary fat | 10–20% of calories | 4–7% | – |
| Running* | 20 miles per wk | 10–15% | – |
| Smoking cessation | Stop 1.5 packs/d | 10% | – |
| Ethanol | 1.3 oz (2.5 drinks) | 10–20% | 6–13% |
| Pharmacologic | | | |
| Niacin ER** | 1,500 mg | 21% | 8–9% |
| Niacin ER | 2,000 mg | 26% | 11–12% |
| Niacin ER/lovastatin | 2,000/40 | 30–41% | 14% |
| Gemfibrozil | 600 mg BID | 6–13% | – |
| Fenofibrate | 134–200 mg | 11–15% | – |
| Pioglitazone | 45 mg | 15% | – |
| Statins | Various | 2–14% | – |

* Other forms of aerobic exercise, such as brisk walking, also raise HDLC.

** Niacin ER is niacin extended-release. Immediate-release or crystalline niacin gives similar HDLC increases. Slow-release niacin is less effective in raising HDLC.

References *(90,125,154–160)*

## CONCLUDING REMARKS

Some clinical observations may help to direct the practitioner toward successful improvement of LDL, triglyceride, and HDL levels in diabetes. (a) It is difficult to get much LDL lowering by diet alone, but we have very good medications to lower LDL. (b) In contrast, medications for hypertriglyceridemia often have limited effects, but dietary treatment accompanied by weight loss sometimes produces extraordinarily good results. (c) Efforts to raise HDL will be much more successful if the practitioner is adept at using niacin and taking advantage of ancillary measures. Some patients, however, have low HDL levels that are highly resistant to treatment, and these patients may benefit from additional reduction of LDL—i.e., targeting the total/HDL cholesterol ratio instead of HDL itself. Lipoproteins play a central role in atherogenesis, and treatment directed at improving the lipoprotein profile in diabetic patients affords a welcome opportunity to prevent or treat their most common serious risk.

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# 18 Management of Coronary Artery Disease in Type 2 Diabetes Mellitus

*John L. Petersen and Darren K. McGuire*

***CONTENTS***



**Summary**

Coronary artery disease (CAD) is the most common cause of death for patients with diabetes mellitus (DM). Patients with CAD and DM constitute roughly one quarter of the total CAD population and are at increased risk of death compared to nondiabetic patients, regardless of the clinical setting. As a consequence, aggressive use of medical and revascularization therapies are appropriate for patients with DM given this increased risk.

Among patients with chronic stable CAD, patients with DM have been demonstrated to benefit from specific therapies, including antiplatelet, renin-angiotensin-aldosterone system (RAAS) antagonists, aggressive blood pressure control, and aggressive lipid management. In addition, attention to angina and evaluation of ischemic symptoms is important in the outpatient management of the diabetic patient with CAD.

Presentation with Acute Coronary Syndromes (ACS) is currently characterized as ST Elevation Myocardial Infarction (STEMI), and Unstable Angina or Non-ST Elevation MI (UA/NSTEMI). Specific characteristics of diabetic patients have been identified among both ACS conditions, and particular benefits have been described from use of antiplatelet and anticoagulation therapies, reperfusion therapy, administration of beta adrenergic and RAAS antagonists, lipid lowering therapy, and revascularization techniques. In general, an aggressive approach to treatment of DM and CAD is recommended for both the stable and ACS populations.

**Key Words:** Coronary artery disease (CAD), acute coronary syndrome (ACS), myocardial infarction (MI), coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI).

## INTRODUCTION

Coronary artery disease (CAD) and its complications are the most common cause of death for patients with diabetes mellitus (DM). Compared to patients without DM, patients with DM and CAD have a higher mortality risk at presentation with acute MI and during long term follow-up *(1–4)*. As a consequence, it is important for providers caring for patients with DM to understand the acute and chronic management of CAD in DM, which is based on the general principles of management of CAD. As most studies of CAD have included patients with DM, considerable knowledge has been gained regarding medical and revascularization treatment in patients with DM. This chapter will discuss the increased risk of DM and CAD, outline the general approach to management of CAD, and highlight specific key recommendations in patients with DM.

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## EPIDEMIOLOGY OF DIABETES MELLITUS AND CORONARY ARTERY DISEASE

The increased cardiovascular disease (CVD) risk associated with DM is well documented in the setting of stable and unstable CAD (Table 1) *(4–20)*. Although most studies of CVD have not distinguished Type 1 and Type 2 DM, most analyses include a large proportion of type 2 DM patients as the prevalence is considerably higher than Type 1 disease *(6)*. In addition, some studies have demonstrated a high incidence of DM among patients presenting with sentinel CAD events, and the prevalence of DM in this setting likely well exceeds current estimates.

DM is associated with increased short- and long-term CVD risk in the setting of unstable CAD. A potentially important interaction between DM and gender had been observed, with diabetic women having an especially poor prognosis. Based on these findings, it is clear that an aggressive approach to secondary prevention is appropriate for optimal management of patients with DM and CAD.

### *Prevalence of Diabetes among Patients with Coronary Artery Disease*

The prevalence of DM ranges from 15–25% among patients presenting with unstable disease *(5,6)*. In addition, a significant number of patients presenting with acute coronary syndromes (ACS) or chronic stable CAD have undiagnosed DM, and some studies have found the incidence of a new diagnosis to be up to 25% of patients at the time of presentation with CAD *(21)*. Thus, given the high prevalence and incidence of DM in CAD populations, routine DM screening should be performed to identify and treat patients with DM when presenting with CAD.

### *Risk of Cardiovascular Events among Patients with Diabetes and Coronary Artery Disease*

#### Diabetes and Cardiovascular Risk in Patients with Stable CAD

Among patients with stable CAD, DM is associated with an increased risk of subsequent CVD events, even in the setting of optimal medical management (Table 1). For example, in both the Scandinavian Simvastatin Survival Study (4S) and the Heart Protection Study (HPS), DM was associated with a significantly increased risk of death and CVD events *(5,6)*. Similarly, in studies of percutaneous coronary intervention (PCI), DM is associated with increased long-term CVD *(7,8)*. In total, these findings demonstrate the increased risk of patients with DM in the outpatient setting and support an aggressive approach to chronic medical therapy.

#### Diabetes and Cardiovascular Risk in Patients with Unstable CAD

In the setting of unstable CAD, patients with DM are at increased risk of death, MI, and stroke immediately following MI and during long term follow up (Table 1). In the First Global Utilization of Streptokinase and Tissue Plasminogen Activator to Open Occluded Coronary Arteries (GUSTO I) trial, a study of 4 thrombolytic strategies for STEMI, 30-d mortality rates were significantly higher for patients with DM *(4)*. Patients with DM in the Second Global Utilization of Strategies to Open Occluded Coronary Arteries (GUSTO IIb) study also had an increased risk of 30-d mortality (adjusted OR 1.75; 95% CI [1.5, 2.1]) and the combined endpoint of death or MI (13.1% versus 8.5%; adjusted OR 1.63; 95% CI [1.4, 1.9]) *(9)*. In the 1st and 2nd Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events post Acute Coronary Syndromes (SYMPHONY) studies, the unadjusted risk of death, MI, or severe recurrent ischemia at 90 d was significantly higher for patients with DM *(10)*. Likewise, in the Second Gruppo Italiano perlo Studio della Soprevvievenza nell'Infarcto Miocardico study (GISSI-2), increased risk of in hospital events was noted in patients with DM *(11)*. Other data sources, such as the pooled analysis from the Fibrinolytic Therapy Trialists (FTT), the Thrombosis in Acute MI (TAMI) studies, and observational data from the Global Registry of Acute Coronary Events (GRACE) also corroborate these findings *(12–17)*.

Increased risk of long-term mortality and CVD events has been demonstrated for patients with DM and unstable CAD. Long-term follow up from the GUSTO I study demonstrated that the initial increase in short-term mortality following STEMI is sustained to at least 1 yr after presentation *(4)*, with similar findings observed during 6 mo of follow-up in the GUSTO IIb study *(9)*, and during 1-yr of follow-up in the SYMPHONY studies *(10)*. Data from the Organization to Assess Strategies for Ischemic Syndromes (OASIS), a large international registry of patients presenting with ACS, has shown an increased risk of death over 2 yr and an increased long-term risk of cardiovascular complications was appreciated among women with DM *(18)*. Analysis of long term events from

Table 1
Risk of Death and Cardiovascular Events Among Diabetic Patients and CAD

| *Trial* | *Population* | *Study Type* | *N Total*<br>*N DM (%)* | *Endpoint* | *Event Rates*<br>*No DM* | <br>*DM* | *Statistical Comparison* |
|---|---|---|---|---|---|---|---|
| 4S | Post MI | Post Hoc<br>RCT Analysis | 4,444<br>202 (4.5) | 5 Yr Mortality | 9.4% | 19.3% | $p < 0.01$ |
| HPS* | High Risk<br>1° Prevention | Prespecifed<br>RCT Analysis | 1,1405<br>1,981 (17.4) | 5 Yr CV Events | 22.7% | 35.6% | $p < 0.01$ |
| TARGET | PCI | Post Hoc<br>RCT Analysis | 4,809<br>1,117 (23.2) | 1 Yr Mortality | 1.6% | 2.5% | $p = 0.056$ |
| ESPRIT | PCI | Post Hoc<br>RCT Analysis | 2,064<br>466 (22.6) | 1 Yr CV Events | 18.4% | 24.5% | $p = 0.008$ |
| GUSTO I | STEMI | Post Hoc<br>RCT Analysis | 41,021<br>5,944 (14.5) | 30 D Mortality | 6.2% | 10.5% | OR 1.77, 95% CI [1.6, 1.9] |
| | | | | 1 Yr Mortality | 8.9% | 14.5% | $p = 0.0001$ |
| GUSTO IIb | ACS | Post Hoc<br>RCT Analysis | 12,142<br>2175 (17.9) | 30 D Mortality<br>6 Mo Death/MI | 8.5%<br>11.4% | 13.1%<br>18.8% | OR 1.75, 95% CI [1.5, 2.1]<br>$p = 0.0001$ |
| SYMPHONY/2nd SYMPHONY | UA/NSTEMI | Post Hoc<br>RCT Analysis | | 90 D CV Events | 9.0% | 11.4% | OR 1.3, 95% CI [1.2, 1.5] |
| | | | | 1 Yr CV Events | 16.7% | 23.8% | OR 1.3, 95% CI [1.1, 1.5] |
| GISSI 2 | STEMI | Post Hoc<br>RCT Analysis | 11,667<br>1838 (15.7) | In-Hospital Mortality | 5.8%a<br><br>13.9%b | 8.7%c<br>10.1%d<br>24.0%c | OR 1.7, 95% CI [0.8, 3.3]<br>OR 2.0, 95% CI [1.6, 2.6]<br>OR 2.2, 95% CI [1.4, 3.5] |
| FTT | STEMI | Metaanalysis | 83,000<br>NA | 30 D Mortality | 7.1% | 11.6% | OR 1.71, 95% CI [1.60, 1.83] |
| TAMI | STEMI | Pooled RCT<br>Analysis | 1,071<br>148 (13.8) | In Hospital Mortality | 6% | 11% | $p$ <0.02 |
| GRACE | ACS | Prospective<br>Registry | 15,000<br>NA | In Hospital Mortality | 6.4%e<br><br>5.1%f<br>2.9%g | 11.7%e<br><br>6.3%f<br>3.9%g | RR 1.48, 95% CI [1.03, 2.13]<br><br>RR 1.14, 95% CI [0.85. 1.52]<br>RR 1.41, 95% CI [1.02, 1.95] |
| OASIS | ACS | Prospective<br>Registry | 8,013<br>1,718 (21.4) | 2 Yr Mortality | 10% | 18% | RR 1.57, 95% CI [1.38, 1.81]j<br>RR 1.28, 95% CI [1.06, 1.56]a,j<br>RR 1.98, 95% CI [1.60, 2.44]b,j |

*(Continued)*

**Table 1**
**(Continued)**

| *Trial* | *Population* | *Study Type* | *N Total*<br>*N DM (%)* | *Endpoint* | *Event Rates*<br>*No DM* | <br>*DM* | *Statistical Comparison* |
|---|---|---|---|---|---|---|---|
| VALIANT | ACS / CHF | Post Hoc | 14,703 | 1 Yr Mortality | 10.9% | 16.2%h | HR 1.50 [1.21, 1.85] |
| | | RCT Analysis | 3980 (27.1) | | | 17.7%i | HR 1.43 [1.29, 1.59] |
| SAVE | CHF | Post Hoc | 2231 | 3.5 Yr Mortality | 20.1% | 31.3% | OR1.39 [1.14, 1.68] |
| | | RCT Analysis | 496 (22.2) | | | | |

*Among population with known CAD in study
[a]Males [b] Females c Insulin Requiring d Noninsulin requiring e STEMI f NSTEMI g UA h New Diagnosis of DM i Previous Diagnosis of DM j adjusted analysis
DM: Diabetes Mellitus
STEMI: ST Elevation Myocardial Infarction
ACS Acute Coronary Syndrome
MI Myocardial Infarction
CHF Congestive Heart Failure
PCI Percutaneous Coronary Intervention
CV Cardiovascular
RCT Randomized Controlled Trial
ACE Angiotensin Converting Enzyme Inhibitor
ARB Angiotensin Receptor Blocker
GUSTO Global Utilization of Streptokinase and Tissue Plasminogen Activator to Open Occluded Coronary Arteries
GISSI Gruppo Italiano perlo Studio della Soprevvievenza nell'Infarcto Miocardico
FTT Fibrinolytic Therapy Trialists
TAMI Thrombolysis and Acute Myocardial Infarction
GRACE Global Registry of Acute Coronary Events
VALIANT Valsartan in Acute Myocardial Infarction Trial
SAVE Survival and Ventricular Enlargement
OASIS Organization to Assess Strategies for Ischemic Syndromes
4S Scandinavian Simvastatin Survival Study
HPS Heart Protection Study
TARGET Do Tirofiban and ReoPro Give Similar Efficacy Outcome Trial
ESPRIT Enhanced Suppression of Platelet IIb/IIIa Receptor with Integrilin Therapy

the Survival and Ventricular Enlargement (SAVE) and Valsartan in Acute MI Trial (VALIANT) studies, which evaluated captopril and valsartan in unstable CAD patients, demonstrated similarly increased CVD risk associated with DM *(19,20)*.

#### Interaction between Sex and DM among Patients with CAD

Some analyses have suggested an interaction between sex and DM, with DM affecting prognosis in women more than men in the setting of ACS. In the Second Gruppo Italiano perlo Studio della Soprevvievenza nell'Infarcto Miocardico study (GISSI-2), in hospital mortality for women with insulin-requiring DM was nearly double that of non-DM patients, with similar observations from registry data including the Worcester Heart Attack Study and the Framingham study *(11,22,23)*. A proposed cause for this interaction is that women with DM are at significantly higher risk of cardiogenic shock and tend to have more extensive CAD than non-diabetic women. Interestingly, analysis from the Second National Registry of MI found an increased prevalence of DM in younger women with MI but no interaction with outcome despite an increased risk of mortality for younger women *(24)*.

#### Epidemiology Conclusions

In sum, most analyses of the DM subgroups from a variety of populations of patients with CAD have found an increased risk of death and cardiovascular events. Although the exact mechanisms remain to be elucidated, it is likely that multiple pathological processes associated with DM contribute to the increased risk of atherosclerosis. Increased platelet aggregation, worse endothelial dysfunction, higher levels of systemic markers of inflammation, and enhanced smooth muscle cell migration have all been demonstrated in patients with DM and likely accelerate the pathogenesis of atherosclerosis *(25–28)*. Optimal management of these patients requires an aggressive and multi-pronged approach to treatment, including aggressive use of antiplatelet, antihypertensive and lipid lowering therapy, in conjunction with appropriate use of revascularization.

## CLINICAL DESCRIPTION AND GENERAL APPROACH TO MANAGEMENT OF STABLE CORONARY ARTERY DISEASE

CAD is a dynamic disease process characterized by prolonged periods of quiescent development and progression of atherosclerotic plaque, with sporadic episodes of acute plaque rupture that can lead to unstable angina or MI. As a consequence, most cardiovascular studies now identify 2 distinct populations: 1) chronic stable CAD, characterized by atherosclerotic disease development and insidious progression that may or may not be associated with clinical symptoms caused by imbalance of myocardial blood supply and demand resulting from a fixed obstructive atherosclerotic lesion; and 2) acute coronary syndromes (ACS), including unstable angina and MI, characterized by an acute clinical presentation caused by the rupture of an unstable coronary artery atherosclerotic plaque with subsequent development of arterial thrombus and impairment of coronary blood flow. The focus of management of patients with stable CAD is risk stratification to guide therapeutic decision-making and the application of interventions to reduce the likelihood of future unstable CAD events.

### *Risk Stratification of Patients with Stable Coronary Artery Disease*

Risk stratification is based on evaluation of clinical symptoms of angina and information derived from cardiac stress testing, and the American Heart Association (AHA) and American College of Cardiology (ACC) have established guidelines for appropriate use of these techniques to evaluate CAD *(29)*. Exercise stress testing on a treadmill continues to be recognized as the best studied modality for evaluating ischemia and provides the most important prognostic information *(30,31)*. The diagnostic accuracy of exercise stress testing can be improved with additional imaging modalities, such as Single Photon Emission Computerized Tomography (SPECT) and transthoracic echocardiography *(29)*. Use of these imaging techniques is important in populations in which the diagnostic accuracy of stress testing is reduced, including female patients and patients with baseline electrocardiographic abnormalities. Patients who are unable to exercise can be stressed pharmacologically with vasodilators such as adenosine or dipyridimole or with dobutamine. Recent advances in stress imaging also include cardiac MRI and CT angiography; however the relationship with prognosis for these tests is less well defined.

Currently, risk stratification with stress testing in asymptomatic patients with DM is controversial. Statistical models have shown that risk of subsequent cardiovascular events among diabetic patients without CAD is similar to non diabetic patients with stable CAD, and up to 20% of asymptomatic patients with DM have abnormalities suggestive of ischemia on myocardial imaging studies *(32)*. Thus some authorities, including the American Diabetes Association (ADA), have suggested that some asymptomatic patients with DM should be routinely screened with stress testing *(33)*. Although prospective studies are ongoing to evaluate the role of routine stress testing in asymptomatic patients with DM, no rigorous studies have been completed to support this recommendation. Furthermore, the best imaging modality for patients with DM remains unclear, and the diagnostic test characteristics in the few head to head studies comparing individual modalities have been discordant. Therefore, no firm recommendation can be made and the routine stress testing of asymptomatic patients with DM is not universally endorsed.

## *Medical Management of Stable Coronary Artery Disease in Patients with Diabetes*

The ACC/AHA Guideline recommendations for patients with stable CAD include therapeutic lifestyle modifications and several classes of medications including antiplatelet therapy, lipid lowering therapy, angiotensin converting enzyme (ACE) inhibitors, beta blockers which have all been shown to reduce CVD risk in DM patients in randomized trials *(34–48)* (Table 2).

### Therapeutic Lifestyle Modification

Therapy to prevent CAD progression and complications is based on a foundation of therapeutic lifestyle modification, including diet, exercise, and smoking abstinence. As described elsewhere in this text, this is especially important among patients with DM and CAD. Although no individual studies have prospectively demonstrated a reduction in CVD risk with lifestyle interventions among DM patients, several prospective randomized controlled trials have demonstrated improvements in cardiovascular fitness and beneficial changes in cardiovascular risk markers associated with such interventions *(49–51)*. In addition, most studies of medical therapy for stable CAD have been conducted with a background recommendation of therapeutic lifestyle modification.

### Antiplatelet Therapy

A fundamental process in the pathogenesis of acute coronary syndromes (ACS) is the formation of arterial thrombus, which involves activation of platelets, subsequent adherence to the vessel wall, and triggering of the coagulation system. Patients with DM have been found to have an increased risk of platelet aggregation caused by decreased sensitivity to intrinsic inhibitors of platelet aggregation, increased fibrinogen and low plasminogen activator inhibitor-type 1 levels, and enhanced secretion of prothrombotic factors *(25,52–54)*. As a consequence, predisposition to platelet aggregation has been proposed as one of the mechanisms to explain the increased risk of cardiovascular events in patients with DM *(54)*.

Several therapies have been developed to antagonize platelet activation and aggregation. The chief antiplatelet effect of aspirin is to irreversibly inhibit cyclooxygenase and thereby inhibit platelet activation mediated by thromboxane A2. The thienopyridines clopidogrel and ticlopidine antagonize the $P2Y_{12}$ component of the adenosine diphosphate (ADP) receptor on the platelet membrane, which inhibits augmentation of the activation response. Among patients presenting with active thrombus and activated platelets, selective antagonism of the glycoprotein IIb/IIIa receptor on the platelet membrane leads to prevention of cross-linking of platelets with fibrin and impairs propagation of arterial thrombus. Each of these therapies has been demonstrated to reduce cardiovascular events and has an appropriate role in the management of CAD and ACS.

**Aspirin in Stable CAD.** Although the results of early studies did not definitively support aspirin use in patients with chronic CAD, convincing evidence for the use of aspirin is provided by the pooled analysis from the Antiplatelet Trialists' Collaboration which combined data from greater than 29,000 patients in 31 randomized, controlled trials of aspirin and other antiplatelet therapies *(55–61)*. Overall, a 15% ($\pm$ 4%; $2p = 0.0003$) relative risk reduction in cardiovascular mortality and 30% relative risk reduction in cardiovascular events was found *(60)*. In subsequent analysis of higher risk patients, a significant reduction of 38 cardiovascular events per 1000 patients with DM was also demonstrated (SD $\pm$ 12; $2p < 0.002$) *(61)*.

**Table 2**
**ACC/AHA guideline recommendations**

*Selected recommendations for medical management of stable CAD*

Aspirin (Class IA)
Clopidogrel if aspirin contraindicated (Class IB)
Beta adrenergic antagonist (Class IA if Prior MI, IB if no Prior MI)
ACE inhibitor (Class IA)
  ARB for ACE inhibitor intolerant patients
Statin agent (LDL $\geq$ 130 mg/dl) (Class IA)
Sublingual nitroglycerin or nitroglycerin spray (Class IB)
Long acting calcium channel antagonists
  Use when betablocker contraindicated (Class IB)
  Use in conjunction with betablocker for refractory angina (Class IB)

*Selected recommendations for management of acute coronary syndromes*
All patients
  Perform 12 lead ECG immediately on presentation (Class IC+)
  Measurement of fasting cholesterol panel (Class IC+)
  Aspirin (Class IA)
    Clopidogrel if aspirin intolerant
    Clopidogrel if CABG not likely (Class IA)
  Angiotensin converting enzyme (ACE) inhibitor
    Initiate within 24 h of admission for anterior infarction,
    pulmonary congestion, or LVEF < 40% (Class IA)
  Beta adrenergic antagonist (Class IA)
  Angiotensin receptor blocker (ARB)
    For patients with ACE inhibitor intolerance (Class IB)
  Aldosterone antagonist
    For patients on a maximum dose of ACE inhibitor or ARB and LVEF<40%, or symptomatic heart failure, or diabetes mellitus (Class IA)
    Nitroglycerin (Class IC)
ST elevation myocardial infarction (STEMI)
  Antithrombin therapy
    Unfractionated heparin (Class IC+)
    Enoxaparin (Class IIA)
  Reperfusion therapy (Class IA)
    Fibrinolysis
    Primary percutaneous coronary intervention
  If primary PCI not performed:
    Coronary angiography for high risk patients (Class IB)
    Stress testing for low risk patients (Class IC+)
Unstable angina/non-st segment elevation myocardial infarction (UA/NSTEMI)
  Antithrombin therapy
    Unfractionated heparin (Class IB)
    Low molecular weight heparin (Class IA)
    Enoxaparin preferable UFH unless CABG planned (Class IIA)
    Fondaparinux (Class Pending)
    Bivalirudin (Class Pending)
  Glycoprotein IIb/IIIa Antagonist (Class IA)
  Coronary angiography for high risk patients (Class IA)
  Stress testing for low risk patients (IC+)

The Early Treatment Diabetic Retinopathy Study (ETDRS) randomized diabetic patients with and without CAD to 325 mg of aspirin twice daily versus placebo and found a strong trend toward reduction in cardiovascular events *(62)*. Although a statistically significant reduction was not found, the study was likely underpowered to detect a reduction in cardiovascular events as less than 10% of patients had known cardiovascular disease. In addition, the ETDRS served as an important safety analysis for aspirin and demonstrated that retinal hemorrhages were not increased with aspirin therapy among diabetic patients. Other support for use of aspirin in diabetic patients comes from the Bezafibrate Infarction Prevention study (BIP) that enrolled 10,954 patients with prior MI; 5 yr cardiovascular mortality was 18.4% and 26.2% among patients with DM treated or not treated with aspirin, respectively (RR 0.8 95% CI [0.7, 0.9]) *(63)*. Based on these data, the ACC /AHA and the ADA guidelines recommend a daily use of aspirin for all patients with DM age > 40 without a specific contraindication to therapy (Table 2).

Although the effectiveness of aspirin in preventing morbidity and mortality in CVD is proven, the appropriate dose of aspirin remains under discussion *(64)*. It is clear from the Antiplatelet Trialists' Collaboration analyses that doses of aspirin exceeding 325 mg daily have no greater CVD risk reduction and may increase bleeding risks compared with lower doses *(65)*, and most studies have evaluated a moderate dose in the range of 75–325 mg *(60,61)*. As a consequence, the dosing of aspirin for CVD prevention reflects the balance among the best studied dose, other conditions that may require aspirin therapy, and the risk of bleeding for an individual patient, with 81–325 mg daily being the most commonly studied doses.

**Thienopyridine Use in Stable CAD.** The most widely studied and most frequently used thienopyridine in clinical practice is clopidogrel, which has been studied in several large randomized controlled trials enrolling sizable subpopulations of patients with DM (Table 3) *(66–73)*. In combination with aspirin, clopidogrel has a critical role following percutaneous revascularization in the prevention of subacute stent thrombosis *(74)*.

Among patients with stable atherosclerotic disease, clopidogrel was studied in the Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial, which randomized patients to 75 mg of clopidogrel versus 325 mg of aspirin daily for a mean follow up of almost 2 yr *(66)*. Overall, a significant reduction was found in the risk of cardiovascular death, MI or stroke, and a statistically significant reduction in the combined rates of ischemic events and bleeding was found in the subgroup with DM. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial enrolled symptomatic and asymptomatic patients with CAD or multiple high risk features and randomized them to treatment with clopidogrel 75 mg daily versus placebo, with both groups treated with daily aspirin *(67)*. Although no overall benefit was appreciated for the primary endpoint of death, stroke or MI, the subgroup of symptomatic patients with known CAD benefited from clopidogrel (6.9% versus 7.9%; RR 0.88 95% CI [0.77 to 0.998]) but a trend toward worse outcome was appreciated the asymptomatic group (6.6% versus 5.5%, $p = 0.20$). Among patients undergoing revascularization, the Clopidogrel for Reduction of Events During Observation (CREDO) study randomized patients to a single 300–600 mg oral loading dose followed by 75 mg daily of clopidogrel versus placebo in addition to aspirin therapy *(68)*. A statistically significant reduction in the combined endpoint of cardiovascular death, MI, stroke and revascularization was found in the overall study, with a similar nonsignificant trend among the DM subset.

Based on these studies, the ACC/AHA Guidelines recommend that clopdiogrel should be used as an alternative therapy for aspirin intolerant patients with stable CAD (Table 2). In addition, high risk patients with CAD also have been shown to benefit from long term use of clopidogrel both following PCI and in the outpatient setting. However, further studies are required to demonstrate whether combination therapy should become the standard of care for all patients with CAD and routine use in addition to aspirin as antiplatelet therapy in high risk primary prevention patients is not currently recommended.

### Antihypertensive Therapy

A number of randomized trials have proven the efficacy of several classes of antihypertensive medications in subsets of patients with DM. Aggressive blood pressure treatment is recommended by all major societies, with a target blood pressure persistently <130/80 mmHg. In patients with CAD, beta adrenergic antagonists and antagonists of the renin-angiotensin-aldosterone system (RAAS) are particularly important because of their documented benefits on subsequent cardiovascular events.

**Beta Adrenergic Antagonists.** Antagonists of the β adrenergic receptor (beta blockers) are also a key component of effective treatment of CAD. In addition to being effective antianginal agents by reducing myocardial

**Table 3**
**Randomized Controlled Trials of Clopidogrel**

| *Trial* | *Population* | *N Total*<br>*N – DM (%)* | *Endpoint* | *Event Rates* | *Statistical Comparison* |
|---|---|---|---|---|---|
| CAPRIE | 2° Prevention | 19,185 | 2 Yr CV Events | 5.83% ASA<br>5.32% Clopidogrel | RRR 0.087 [0.003, 0.165] |
| | | 3866 (20.1) | 2 Yr CV Events and Bleeding | 17.7% ASA<br>15.6% Clopidogrel | RRR 0.125 |
| CURE | UA/NSTEMI | 12,562 | 1 yr CV Event | 11.4%% ASA<br>9.3% ASA/Clopidogrel | RR 0.80 [0.72, 0.90] |
| | | 2840 (22.6) | 1 yr CV Event | 16.7% ASA<br>14.2% ASA/Clopidogrel | $p$ = NS |
| CREDO | UA/NSTEMI | 2116 | 1 Yr CV Events | 11.5% ASA<br>8.5 % ASA/Clopidogrel | RRR 0.269 [0.039, 0.444] |
| | | 560 (26.4) | 1 Yr CV Events | NA<br>NA | RRR 0.112, [0.462, −0.468] |
| CLARITY | STEMI | 3491<br>NA | TIMI 1 Flow or Recurrent MI | 21.7% ASA<br>15.9% ASA/Clopidogrel | ORR 0.36 [0.24, 0.47] |
| CHARISMA | High Risk 1° and 2° Prevention | 15,063<br>6556 (43.5) | Death, MI or Stroke | 7.3% ASA<br>6.8% ASA/Clopidogrel | RR 0.93 [0.83, 1.05] |
| COMMIT | All ACS | 45,852<br>NA | 2 Wk CV Events | 10.1% ASA<br>9.2% Clopidogrel | RRR 0.09 [0.03, 0.16] |

DM Diabetes Mellitus
MI Myocardial Infarction
RR Relative Risk
RRR Relative Risk Reduction
ORR Odds Ratio Reduction
ASA Aspirin
NS Not Significant
NA Not Available
CV Cardiovascular
CAPRIE Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events
CURE Clopidogrel in Unstable Angina to Prevent Recurrent Events
CREDO Clopidogrel for Reduction of Events During Observation
CLARITY Clopidogrel as Adjunctive Reperfusion Therapy
CHARISMA Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
COMMIT Clopidogrel and Metoprolol in Myocardial Infarction Trial

Table 4
Randomized Controlled Trials of Beta Blocker Therapy for CAD

| *Trial* | *Population* | *Yr* | *N Total*<br>*N–DMC (%)* | *Endpoint* | *Event Rates* | *Statistical Comparison* |
|---|---|---|---|---|---|---|
| MIAMI | Post MI | 1981 | 5778 | 15 D Mortality | 4.9% Placebo<br>4.3% Metoprolol | RRR 0.13%, $p = 0.29$ |
| | | | 413 (7.1) | 15 D Mortality | 11.3% Placebo<br>5.7% Metoprolol | RRR 36.8%, $p = 0.06$ |
| BHAT | Post MI | 1982 | 3837 | 2 Yr Mortality | 9.8% Placebo<br>7.2% Propranolol | RRR 26.5%, $p < 0.005$ |
| | | | 441 (11.5) | 2 Yr Mortality | 14.4% Placebo<br>9.3% Propranolol | RRR 35.4%, $p =$ NS |
| Norwegian Timolol | Post MI | 1982 | 1884 | 17 Mo Mortality | 21.9% Placebo<br>13.3% Timolol | RRR 60.6%, $p = 0.0003$ |
| | | | 99 (5.2) | 17 Mo Mortality | 30.5% Placebo<br>11.3% Timolol | RRR 62.8%, $p < 0.05$ |
| Göteborg | Post MI | 1983 | 1395 | 90 D Mortality | 8.9% Placebo<br>5.7% Metoprolol | RRR 0.36%, $p < 0.03$ |
| | | | 120 (8.6) | 90 D Mortality | 17.9% Placebo<br>7.5% Metoprolol | RRR 0.58%, $p = 0.16$ |
| | | | | 90 D MI | 16.4% Placebo<br>3.8% Metoprolol | RRR 0.77%, $p < 0.05$ |
| ISIS 1 | UA/NSTEMI | 1986 | 16,027 | 7 D CV Mortality | 4.57% Placebo<br>3.89% Atenolol | RRR 14.9%, $p < 0.04$ |
| | | | 958 (6.0) | 7 D CV Mortality | 8.1% Placebo<br>6.3% Atenolol | RRR 23.3%, $p =$ NS |
| COMMIT | Post MI | 2005 | 45,852 | In Hospital Mortality | 7.8% Placebo<br>7.7% Metoprolol | OR 0.99 [0.92, 1.05] |

DM Diabetes Mellitus
MI Myocardial Infarction
CV Cardiovascular
RRR Relative Risk Reduction
OR Odds Ratio
NS Not Significant
MIAMI Metoprolol in Acute Myocardial Infarction
BHAT Betablocker Heart Attack Trial
ISIS International Study of Infarct Survival
COMMIT Clopidogrel and Metoprolol in Myocardial Infarction Trial

oxygen demand through negative chronotropic and inotropic effects, multiple studies have demonstrated a mortality benefit from beta blockers in post MI patients (Table 4) *(75–84)*. Among studies of long term beta blocker use in stable CAD patients, a significant reduction in death and MI was found over 17 mo in the diabetic patients enrolled in the Norwegian timolol study and a similar trend was noted with propranolol in the Beta blocker Heart Attack Trial (BHAT) (Table 4) *(75,76)*. These findings are supported by a post-hoc analysis of 2,723 diabetic patients in the BIP, which found a significant reduction in mortality associated with beta blockers after adjusting for covariates (RR 0.58, 95% CI [0.44, 0.77]) *(85)*.

During the early studies with beta blockers, concern arose regarding their use in diabetic patients caused by fears of masking hypoglycemic events, interference with insulin release, and inhibition of gluconeogenesis *(85)*. Subsequent analyses of hypoglycemic symptoms with therapeutic doses of beta blockers have demonstrated that while heart pounding and tremor may be diminished, increased perspiration has been noted among patients with hypoglycemic events treated with beta blockers. However, no increased mortality caused by hypoglycemic events has been reported among patients with DM prescribed beta blockers *(83)*. Concerns also have been raised about beta blockers in patients with chronic congestive heart failure, but it is now clear that use of these agents is especially beneficial in this population owing to beneficial effects on the neuro-endocrine mechanisms involved in heart failure *(87)*. Because of these effects and benefits, beta blockers have been classified as a Class I therapy for treatment of chronic CAD for all patients by the ACC/AHA guidelines.

**Renin-Angiotensin-Aldosterone Antagonists.** Although RAAS antagonists have an important role in renal protection for patients with DM, benefit has also been appreciated from these agents in patients with cardiovascular disease. Reduction in angiotensin II (AT-II) levels can be achieved with ACE inhibitors, selective inhibition of the effects of AT-II can be mediated by angiotensin receptor blockers (ARB), and the effects of aldosterone can be antagonized by spironolactone and eplerenone. The inhibition of the catabolism of bradykinin by ACE inhibitors has been demonstrated to cause some limiting side effects, including cough and angioedema, but some have hypothesized that increased levels of bradykinin may also contribute to a net benefit in the cardiovascular system *(88)*. All of these agents have a role in the management of cardiovascular disease in general and particularly among patients with DM.

Studies of patients with heart failure, cardiovascular disease, and DM have demonstrated that RAAS antagonists may have effects on clinical events that cannot be solely attributed to reduction of blood pressure (Table 5)

**Table 5**
**Randomized Controlled Trials of ACE Inhibitors and Angiotensin Receptor Blockers**

| *Trial* | *Population* | *N – Total*<br>*N – DM (%)* | *Endpoint* | *Event Rates* | *Statistical Comparison* |
|---|---|---|---|---|---|
| CONSENSUS | Chronic CHF | 253 | 6 Mo | 44% Placebo | RRR 40%, $p = 0.0002$ |
| | | 45 (17.8) | Mortality | 26% Enalapril | |
| V-HeFT II | Chronic CHF | 804 | 2 Yr | 25% Hydral/Nitrate | RRR 28%, $p = 0.016$ |
| | | 164 (20.3) | Mortality | 18% Enalapril | |
| SOLVD | Chronic CHF | 2569 | 41 Mo | 39.7% Placebo | RRR 16% [5, 26] |
| Treatment | | 663 (25.8) | | 35.2% Enalapril | $p = 0.0036$ |
| SOLVD | EF <35% | 4228 | 3 Yr | 15.8% Placebo | RRR 8% [−8, 21] |
| Prevention | Asymptomatic | 647 (15.3) | Mortality | 14.8% Enalapril | $p = 0.30$ |
| TRACE | Post ACS | 1749 | 3 Yr | 42.3% Placebo | RR 0.78 [0.67, 0.91] |
| | With CHF | | Mortality | 34.7% Trandolapril | |
| | | 237 (13.6) | 26 Mo | 61% Placebo | RR 0.64 [0.45, 0.91] |
| | | | Mortality | 45% Trandolapril | |
| SAVE | Post MI | 2231 Total | 42 Mo | 25% Placebo | RRR 19% [3, 32] |
| | With CHF | 44 (2.0) | Mortality | 20% Captopril | |
| GISSI-3 | Post MI | 19,394 | 6 Wk | 7.1% Placebo | OR 0.88 [0.79, 0.99] |
| | | | Mortality | 6.3% Lisinopril | |
| | | 2790 (14.4) | | 12.4% Placebo | OR 0.68 [0.53,0.86] |
| | | | | 8.7% Lisinopril | |

(*Continued*)

Table 5
(Continued)

| *Trial* | *Population* | *N – Total*<br>*N – DM (%)* | *Endpoint* | *Event Rates* | *Statistical Comparison* |
|---|---|---|---|---|---|
| ISIS-4 | Post MI | 58,050 | 5 Wk<br>Mortality | 7.69% Placebo<br>7.19% Captopril | ORR 7% [1, 13]<br>$p = 0.02$ |
| CONSENSUS II | Post MI | 6090<br>685 (11.2) | 6 Mo<br>Mortality | 10.2% Placebo<br>11.0% Enalapril | RR 1.10 [0.93, 1.29] |
| AIRE | Post MI<br>With CHF | 2006<br>240 (12.0) | 15 Mo<br>Mortality | 23% Placebo<br>17% Ramipril | RRR 27% [11, 40]<br>$p = 0.002$ |
| CCS-1 | Post MI<br>With CHF | 14,962 | 4 Wk<br>Mortality | 9.74% Placebo<br>9.12% Captopril | $p = 0.20$ |
| ELITE-1 | CHF | 722<br>183 (25.3) | 48 Wk<br>Mortality | 13.2% Captopril<br>9.4% Losartan | RRR 46% [5, 69] |
| ELITE-2 | CHF | 3152<br>749 (23.8) | 1.5 Yr<br>Mortality | 15.9% Captopril<br>17.7% Losartan | HR 1.13 [0.95, 1.35]<br>$p = 0.016$ |
| Val-HeFT | CHF | 5010<br>1277 (25.5) | 2 Yr<br>Mortality | 19.4% Placebo<br>19.7% Valsartan | |
| CHARM<br>Overall | CHF | 7601<br><br>2160 (28.4) | 3 Yr<br>Mortality | 23% Placebo<br>25% Candesartan<br>46.0% Placebo<br>43.2% Candesartan | HR 0.91 [0.83, 1.00]<br>$p = 0.055$<br>$p$ = NS |
| OPTIMAAL | Post ACS<br>With CHF | 5477<br>940 (17.2) | 2.7 Yr<br>Mortality | 16% Captopril<br>18% Losartan | RR 1.13, [0.99, 1.28] |
| VALIANT | Post ACS<br>With CHF | 14,703<br>3400 (23.1) | 2 Yr<br>Mortality | 19.5% Captopril<br>19.9% Valsartan<br>19.3% Captopril & Valsartan | <br>HR 1.00 [0.90, 1.11]<br>HR 0.98 [0.89, 1.09] |
| HOPE | High Risk DM<br>or CV Disease | 9297<br><br>3577 (38.5) | 5 Yr CV<br>Death, MI<br>Or Stroke | 17.8% Placebo<br>14.0% Ramipril<br>19.8% Placebo<br>15.3% Ramipril | RR 0.78 [0.70, 0.86]<br><br>RRR 25% [12%, 36%] |

DM Diabetes Mellitus
MI Myocardial Infarction
CV Cardiovascular
ACS Acute Coronary Syndrome
CHF Congestive Heart Failure
EF Ejection Fraction RR Relative Risk
RRR Relative Risk Reduction
OR Odds Ratio
HR Hazard Ratio
NS Not Significant
Hydral Hydralazine
CONSENSUS Cooperative North Scandinavian Enalapril Survival Study
V-HeFT Vasodilator Heart Failure Trial
SOLVD Study of Left Ventricular Dysfunction
TRACE Trandolapril Cardiac Evaluation
SAVE Suvival and Ventricular Enlargement
GISSI Gruppo Italiano perlo Studio della Soprevvievenza nell'Infarcto Miocardico
ISIS International Study of Infarct Survival
AIRE Acute Infarction Ramipril Efficacy
CCS Chinese Captopril Study
ELITE Evaluation of Losartan in the Elderly
Val-HeFT Valsartan Heart Failure Trial
CHARM Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality
OPTIMAAL Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan
VALIANT Valsartan in Acute Myocardial Infarction Trial
HOPE Heart Outcomes Prevention Evaluation

*(89–110)*. Although combination therapy of ARBs and ACE inhibitors has not been demonstrated to provide incremental benefit in terms of cardiovascular events, ARBs have been demonstrated to be an effective alternative among ACE inhibitor intolerant patients with cardiovascular disease *(110–112)*. Interestingly, in the Antihypertensive and Lipid-Lowering Treatment to prevent Heart attack (ALLHAT) trial that compared various strategies of antihypertensive regimens in general population of patients with hypertension, a reduction in cardiovascular events from the ACE inhibitor lisinopril was not appreciated *(113)*. This finding suggests that inhibition of the RAAS may be more critical in the setting of atherosclerosis, heart failure, and DM than in isolated hypertension.

*Angiotensin Converting Enzyme Inhibitors* Among patients with DM, the benefit from ACE inhibitors in progression of diabetic nephropathy has been well established, and inhibition of the RAAS should already be prescribed for many known diabetic patients presenting with CAD. However, particular benefit has been demonstrated from ACE inhibitors among diabetic patients presenting with both ACS and atherosclerotic heart disease *(43)*.

The initial large clinical outcomes studies of ACE inhibitors were performed in patients with congestive heart failure and reduced left ventricular function *(89–91)*. Although the initial studies in heart failure found dramatic effects on mortality both in the short term and over the long term, the number of diabetic patients enrolled in both of these landmark studies are too few to be considered for subgroup analysis. The Study of Left Ventricular Dysfunction Prevention and Treatment Trials (SOLVD-P and SOLVD-T) demonstrated a significant reduction in mortality among symptomatic patients and a reduction in deaths owing to progression to heart failure in asymptomatic patients *(92,93)*. Approximately one fifth of the patients enrolled in these studies had DM, and although DM increased the risk of mortality, a similar benefit was noted among diabetic and nondiabetic patients from treatment with enalapril *(94)*.

More direct evidence of the effect of ACE inhibitors in diabetic patients comes from the Heart Outcomes Prevention Evaluation (HOPE) study, which randomized patients with normal ventricular function and DM or known stable cardiovascular disease and one additional risk factor in a $2 \times 2$ factorial design to ramipril and vitamin E *(95)*. Overall, a significant reduction in cardiovascular events was found with ramipril, and this benefit was also noted in the diabetic subgroup as well, supporting the routine use of ACE inhibitors in diabetic patients *(41)*. In addition, a reduction in the combined incidence of diabetic nephropathy, requirement for dialysis, and photocoagulation for complications of diabetic retinopathy was also significantly reduced.

In summary, solid evidence exists for the use of ACE inhibitors in patients with DM and cardiovascular disease, left ventricular dysfunction, or diabetic nephropathy. Importantly, the benefit appreciated from ACE inhibitors in broader CAD populations also is noted among diabetic patients, giving support to their continued use after diagnosis of atherosclerotic heart disease. As a consequence, ACE inhibitors have been given a Class I recommendation for the treatment of ACS and chronic CAD patients in patients without significant contraindications.

*Angiotensin Receptor Blockers* Although the data for reducing cardiovascular events in diabetic patients are very strong with ACE inhibitors, many patients are intolerant of ACE inhibitors owing to severe renal insufficiency, a bradykinin-induced cough, angioedema, or other side effects. Although the benefit of adding an ARB to existing therapy with an ACE inhibitor has not been demonstrated, the ARBs are an attractive alternative for patients who are intolerant to ACE inhibitors.

The initial studies with ARBs evaluated patients with heart failure predominantly due to CAD. In studies with direct comparisons to ACE inhibitors, inconsistent results have been demonstrated among the Evaluation of Losartan in the Elderly (ELITE) studies that compared captopril with valsartan in elderly patients with heart failure *(105)*. Although valsartan appeared to be superior to captopril to reduce all cause mortality in ELITE, this finding was not confirmed in the larger and more definitive ELITE II study *(106)*.

Studies of combination therapy with ACE inhibitors and ARBs also have yielded conflicting results. The Valsartan Heart Failure Trial (Val-HEFT) randomized patients with heart failure to valsartan or placebo, on top of a background therapy with an ACE inhibitor *(109)*. Although the combined primary endpoint of death, resuscitation from arrest, use of inotropic therapy and admission with heart failure was reduced, most of the benefit was observed in the minority of patients not prescribed ACE inhibitors in the placebo arm. In addition, an adverse interaction was observed for patients on beta blocker and combination ACE inhibitor and ARB therapy. In the Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality (CHARM) clinical trial program, overall a benefit was appreciated from candesartan among heart failure patients. Although no difference was found in the diabetic patients, the small sample size suggests that this subgroup is likely underpowered to

detect any benefit *(107)*. A component of the CHARM program, the CHARM added trial, compared patients on an ACE inhibitor and a beta blocker and randomized them to candesartan versus placebo *(110)*. A statistically significant reduction in cardiovascular death and hospitalization for heart failure was appreciated and, based on this finding, some authorities recommend dual therapy for patients with heart failure that is refractory to ACE inhibitor therapy alone.

Although a specific analysis of the benefits of ARBs in diabetic patients was not conducted in CHARM added, analysis of the entire CHARM database has demonstrated that DM is among the most powerful predictors of mortality in heart failure patients *(113)*. This association was consistent, regardless of background therapy with ACE inhibitors and beta blockers.

In general, the data do not support routine use of dual therapy with an ACE inhibitor and an ARB for patients with stable CAD or ACS alone. However, ARBs are recommended for patients who are intolerant of ACE inhibitors. This recommendation is supported by subgroup data from Val-HEFT among patients not prescribed ACE inhibitors, and the findings of the CHARM-Alternative trial that demonstrated a significant reduction in cardiovascular events compared with placebo in ACE inhibitor intolerant patients.

### Dyslipidemia Therapy

A key advance in the management of CAD has been the recognition of the importance of dyslipidemia in the development of atherosclerosis and the subsequent risk of future events. The association of elevated levels of low-density lipoprotein (LDL) cholesterol and low levels of high-density lipoprotein (HDL) cholesterol with risk of atherosclerosis has been well established and multiple clinical trials have demonstrated the importance of identifying patients with dyslipidemia and instituting appropriate therapy *(114,115)*. Patients with DM and cardiovascular disease are among the highest risk group of patients, and current recommendations are for very aggressive lipid lowering therapy with a target LDL cholesterol of less than 70 mg/dl *(116,117)*.

In contrast to LDL and HDL cholesterol, the association of elevated triglycerides with atherosclerosis has been recognized in some population-based analyses but not others *(118,119)*. The association among abnormal glucose metabolism, low levels of HDL cholesterol, high fasting triglyceride levels, hypertension, and abdominal obesity and its contribution to cardiovascular risk has been recognized *(120)*. Although statin therapy remains the mainstay of cholesterol management, some patients have fasting cholesterol profiles that suggest other types of lipid lowering therapy may be important.

Chapter X provides a detailed discussion of lipid management in patients with DM.

## CORONARY REVASCULARIZATION OF THE PATIENT WITH DIABETES MELLITUS

For many patients, medical therapy alone is not adequate to relieve symptoms or to optimize risk of future CVD events. Some types of stenoses such as left main coronary artery or proximal left anterior descending (LAD) disease, when they become unstable, can be severe enough to cause hemodynamic instability and cardiac arrest. In other cases, revascularization may not be associated with a reduction in mortality, but may be associated with a reduction in other CAD manifestations, including angina. The current standard for evaluating the need for coronary revascularization is coronary angiography. For most patients, coronary angiography is a safe procedure and improvements in the equipment and radiographic contrast media have dramatically improved the safety of the procedure in recent years *(121)*. The current risk of death associated with angiography is approximately one in one-thousand cases, and typically patients with left main disease and severe aortic stenosis are among the patients with the highest risk of death during coronary angiography *(122)*. Other useful information that may be gathered at the time of catheterization include an assessment of left ventricular function with ventriculography, measurement of intracardiac pressures and cardiac output, and assessment of valvular abnormalities. Although other imaging modalities such as CT angiography and cardiac MRI have been developed to assess ischemic heart disease, these techniques currently do not provide enough detail for appropriate decisions regarding revascularization. Hence, the current approach to revascularization is based on interpretation of the coronary angiograms and incorporating important clinical characteristics of the patient. Two general approaches are available for revascularization: 1) Coronary Artery Bypass Grafting (CABG), and 2) Percutaneous Coronary Intervention (PCI).

Table 6
Randomized controlled trials of coronary artery bypass surgery versus medical therapy versus percutaneous coronary intervention

| *Trial* | *Population* | *N - Total*<br>*N – DM (%)* | *End Point* | *Event Rates* | *Statistical Comparison* |
|---|---|---|---|---|---|
| European Coronary Surgery Study | Single and Multivessel CAD | 767<br>46 (6.0) | 5 Yr Mortality | 16.9% Medical<br>7.6% CABG | $p = 0.0001$ |
| | | | 12 Yr Mortality | 33.3% Medical<br>29.4% CABG | $p = 0.04$ |
| CASS | Single and Multivessel CAD | 780 - Total<br>86 (8.7) | 5 Yr Mortality | 9.2% Medical<br>7.4% CABG | $p$ = NS |
| VA Bypass Surgery Study | Single and Multivessel CAD | 686<br>86 (12.5) | 7 Yr Mortality | 30 % Medical<br>23 % CABG | $p = 0.043$ |
| | | | 11 Yr Mortality | 43% Medical<br>42% CABG | $p$ = NS |
| MASS | LAD CAD | 142<br>38 (26.8) | 3.5 Yr CV Death, MI, RR from Angina | 17.0 % Medical<br>3.0% CABG | $p = 0.006$ |
| MASS II | Multivessel CAD | 406<br>65 (16.0) | 1 Yr Mortality | 1.5 % Medical<br>4.0 % CABG | $p = 0.23$* |
| | | | 1 Yr Death, MI, RR from Angina | 7.2% Medical<br>6.4% CABG | $p$ = NS |
| BARI | Multivessel CAD | 1829 | 5 Yr Mortality | 10.7% CABG<br>13.7% PTCA | $p = 0.19$ |
| | | 353 (19.3%) | 5 Yr Mortality | 19.4% CABG<br>34.5% PTCA | RR 1.87 [1.24, 2.82] |
| EAST | Multivessel CAD | 392<br>90 (23.0) | 8 Yr Mortality | 17.3 % CABG<br>20.7 % PTCA | $p = 0.40$ |
| | | | 3 Yr Death, MI, Thallium Defect | 27.3% CABG<br>28.8% PTCA | $p = 0.81$ |
| GABI | Multivessel CAD | 359<br>46 (12.8) | 1 Yr Mortality | 6.5% CABG<br>2.6% PTCA | $p$ = NS |
| | | | Freedom From Angina | 74% CABG<br>71% PTCA | $\Delta$ 3% $\pm$ 10%, p = NS |
| RITA | Single and Multivessel CAD | 1011<br>NA | 2.5 Yr Mortality | 3.6% CABG<br>3.1% PTCA | $p$ = NS |
| | | | 2.5 Yr Death or MI | 8.5% CABG<br>9.8% PTCA | RR 0.88; 95% CI [0.59, 1.29] |

*(Continued)*

**Table 6**
**(Continued)**

| *Trial* | *Population* | *N - Total*<br>*N – DM (%)* | *End Point* | *Event Rates* | *Statistical Comparison* |
|---|---|---|---|---|---|
| | | | 5 Yr Mortality | 9.0% CABG<br>7.6% PTCA | $p = 0.51$ |
| | | | 5 Yr Death or MI | 11.1% CABG<br>14.1% PTCA | Δ 3%; 95% CI [21.0, −7.1%] |
| Tolouse | Multivessel CAD | 152 | 5 Yr Mortality | 10.5% CABG<br>13.2% PTCA | $p$ = NS |
| ERACI | Multivessel CAD | 127<br>14 (11.0) | 3 Yr Mortality | 4.7% CABG<br>9.5% PTCA | $p = 0.5$ |
| | | | 3 Yr Death, MI Angina, Revasc | 23% CABG<br>53% PTCA | $p < 0.0005$ |
| MASS | LAD<br>CAD | 142<br>33 (23.2) | 3.5 Yr CV Death, MI, Revasc/Angina | 3.0% CABG<br>24.0% PTCA | $p = 0.0002$ |
| Lausanne | LAD<br>CAD | 134<br>24 (17.9) | 5 Yr Mortality | 3% CABG<br>9% PTCA | $p = 0.12$ |
| | | | 5 Yr CV Death MI or Revasc | 14% CABG<br>44% PTCA | RR 4.2 95% CI [2.8, 5.6] |
| CABRI | Multivessel CAD | 1054 | 1 Yr Mortality | 2.7% CABG<br>3.9% PTCA | RR 1.42 95% CI [0.73, 2.76] |
| | | | 4 Yr Mortality | 7.4% CABG<br>10.9% PTCA | RR 1.47 95% CI [0.99, 2.19] |
| | | 125 (11.4) | 4 Yr Mortality | 12.5% CABG<br>22.6% PTCA | RR 1.81 95% CI [0.80, 4.08] |
| SoS | Multivessel CAD | 988<br>142 (14.3) | 1 Yr | 2% CABG<br>5% PCI | HR 2.91 95% CI [0.63, 1.42] |
| ERACI II | Multivessel CAD | 450<br>78 (17.3) | 1.5 Yr Mortality | 7.5 % CABG<br>3.1 % PCI | $p < 0.017$ |
| | | | 5 Yr Mortality | 11.5% CABG<br>7.1% PCI | $p = 0.182$ |
| | | | 5 Yr Death, MI Stroke, Revasc | 23.6% CABG<br>34.7% PCI | $p < 0.019$ |
| ARTS | Multivessel CAD | 1205 | 5 Yr Mortality | 7.6 % CABG<br>8.0 % PCI | RR 1.05 95% CI [0.71, 1.55] |
| | | | 5 Yr Death, MI Stroke | 14.9 % CABG<br>18.2 % PCI | RR 1.22 95% CI [0.95, 1.58] |
| | | 208 (17.3) | 5 Yr Mortality | 8.3 % CABG | RR 1.61 95% CI [0.71, 163] |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 13.4% PCI | |
| | | | 5 Yr Death, MI Stroke | 19.8 % CABG<br>25.0 % PCI | RR 1.26 95% CI [0.76, 2.11] |
| AWESOME | Multivessel CAD | 454 | 3 Yr Mortality | 21% CABG<br>20% PCI | $p$ = NS |
| | | | 3 Yr Death or RR for Angina | 39% CABG<br>52% PCI | Δ 13%, SE ±5%, p < 0.001 |
| | | 144 (31.5) | 3 Yr Mortality | 28% CABG<br>19% PCI | Δ 9%, SE ±9%, p < 0.27 |
| SIMA | Single Vessel CAD | 121<br>15 (12.4) | 2.4 Yr Mortality | 1.6% CABG<br>0.8% CABG | $p$ = NS |
| | | | 2.4 Yr Death, MI, or Revasc | 7% CABG<br>31% PCI | RR 4.0; 95% CI [2.0, 6.0] |
| Leipzig | Single Vessel CAD | 220<br>65 (29.5) | 0.5 Yr CV Mortality | 1.8% CABG<br>0.0% PCI | $p$ = NS |
| | | | 0.5 Yr CV Death, MI or Revasc | 14.8% CABG<br>31.5% PCI | |
| MASS II | Multivessel CAD | 408<br>52 (12.7) | 1 Yr Mortality | 4.0 % CABG<br>4.4 % PCI | $p$ = 0.23* |
| | | | 1 Yr Death, MI, Revasc/Angina | 6.4% CABG<br>24.4% PCI | $p$ < 0.0001 |

Abbreviations:
CAD: Coronary Artery Disease
MI: Myocardial Infarction
CABG: Coronary Artery Bypass Surgery
PCI: Percutaneous Coronary Intervention
PTCA Percutaneous Transluminal Coronary Angioplasty
RR: Relative Risk
Revasc: Repeat Revascularization
Revasc/Angina: Repeat Revascularization due to Angina
CASS: Coronary Artery Surgery Study
MASS: Medicine, Angioplasty or Surgery Study
BARI: Bypass Angioplasty Revascularization Investigation
EAST: Emory Angioplasty versus Surgery Trial
GABI: German Angioplasty Bypass surgery Investigation
RITA: Randomized Intervention Treatment of Angina
CABRI: Coronary Angioplasty versus Bypass Revascularization Investigation
ERACI: Argentine Randomized Trial of Percutaneous Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease
SoS: Stent or Surgery Trial
ARTS: Arterial Revascularization Therapies Study
AWESOME: Angina with Extremely Serious Operative Mortality Evaluation
SIMA: Stenting versus Internal Mammary Artery Trial

### Initial Studies Supporting Use of CABG

CABG was adopted as a standard of care for revascularization compared with standard medical therapy based on data from 3 randomized controlled trials conducted in the 1970s and 1980s (Table 6). A mortality benefit was demonstrated at 5 yr in the European Coronary Surgery Study, but overall neither the Coronary Artery Surgery Study (CASS) nor the VA Coronary Artery Bypass Surgery Cooperative Group Study demonstrated a clear reduction in mortality *(123–126)*. However, pooled analyses of these studies have demonstrated a reduction in long term mortality for patients with left main coronary disease, 3-vessel coronary artery disease, or proximal LAD disease *(127)*. In addition, patients with mild to moderate impairment of left ventricular function had a significantly improved survival at 5 yr following CABG compared with medical therapy alone, and conversely most patients with normal ventricular function and 1 or 2 vessel CAD did not benefit from CABG.

However there are some key limitations of these data to current practice. Patients with ejection fractions <35% were excluded from the studies and very few women were enrolled. In addition the studies were conducted in an era with different standards of medical treatment and before development of percutaneous coronary intervention (PCI). Although more recent trials of revascularization have been conducted to evaluate CABG in more contemporary practice patterns, the initial studies and pooled analyses continue to serve as the foundation for the recommendations for the ACC /AHA guidelines for CABG *(128)*.

## *Percutaneous Coronary Intervention*

### Coronary Stenting and Restenosis

**Coronary Stenting with Bare Metal Stents.** Restenosis of treated lesions is a considerable problem following PCI, especially in patients with DM. Following standard balloon angioplasty alone, elastic recoil and arterial dissection following balloon dilation was a considerable limitation and frequently lead to repeat procedures. An important advance in PCI was the development of intracoronary stents, which significantly reduce in abrupt vessel closure during and immediately after angioplasty (Table 7) *(129,130)*. The first generation of stents used in practice were simple bare metal stents (BMS) mounted on and delivered by balloon catheters. Although stenting dramatically decreased the need for repeat revascularizations, patients frequently developed restenosis several months after implantation. In contrast to elastic recoil, histopathologic studies found that in stent restenosis (ISR) is caused by neointimal hyperplasia, a process in which proliferation of extracellular matrix occurs at the target lesion site mediated by smooth muscle cells and other inflammatory mediators. Based on this understanding, a newer generation of drug eluting stents (DES) have been developed that locally deliver medications to inhibit the proliferation of extracellular matrix and smooth muscle cells.

Although the clinical benefit from stenting has been demonstrated in the broad population of patients undergoing PCI, proof that BMS implantation is associated with benefit for diabetic patients has been more difficult to establish. The initial studies with coronary stents included too few diabetic patients to draw definitive conclusions about their effect in this subgroup *(129–133)*. However, several registries and retrospective reviews noted an increased rate of restenosis in diabetic patients following stent implantation compared with nondiabetic patients *(134–140)*. Similar findings have been noted in analyses of diabetic subgroups from randomized controlled trials *(141)*. In the Stent-Percutaneous Angioplasty for Acute MI trial (Stent-PAMI), a randomized controlled trial comparing stenting with balloon angioplasty alone for primary PCI of STEMI, similar angiographic restenosis rates were found in diabetic patients treated with a stent or standard balloon angioplasty *(142,143)*. Diabetic patients in the Intracoronary Stenting of Angioplasty for Restenosis Reduction in Small Arteries (ISAR-SMART) trial had a 45% angiographic restenosis rate following PCI of lesions in both the stent implantation and standard balloon angioplasty arms *(144)*. For patients undergoing PCI in general, analysis from the Prevention of Restenosis with Tranilast and Its Outcomes Trial (PRESTO) found key predictors for restenosis are lesion length, lesion complexity, target vessel diameter, prior percutaneous intervention, DM and tobacco use *(145)*. Among diabetic patients, key predictors also include glycemic control, and use of coronary stenting, and observational studies have demonstrated that glycemic control defined as a hemoglobin A1c $\leq$ 7% is associated with a reduction repeated revascularizations and other cardiovascular events *(146,147)*.

**Coronary Stenting with Drug Eluting Stents.** To address the problem of ISR, the most recent advance in coronary stenting is the development of drug delivery systems applied to the stent that are intended to directly

Table 7
Randomized Controlled Trials of Percutaneous Coronary Interventions: Balloon Angioplasty, Bare Metal Stents, Drug Eluting Stents and Brachytherapy

| *Trial* | *Population* | *N - Total*<br>*N – DM (%)* | *End Point* | *Event Rates* | *Statistical Comparison* |
|---|---|---|---|---|---|
| BENESTENT | Lesion ≤ 15 mm<br>Vessel ≥ 3.0 mm | 516<br>34 (6.6) | 7 Mo Death, MI<br>Stroke or Revasc | 30% PTCA<br>20% PS Stent | RR 0.58; [0.40, 0.85]; p = 0.005 |
| | | 516 | 7 Mo<br>Restenosis ≥ 50% | 32% PTCA<br>22% PS Stent | p = 0.02 |
| BENESTENT II | Lesion ≤ 15 mm<br>Vessel ≥ 3.0 mm | 827<br>99 (11.9) | 6 Mo Death, MI<br>or Revasc | 19.3% PTCA<br>12.8% Hepacoat PS Stent* | RR 0.67; [0.48, 0.92]; p < 0.001 |
| | | 416 | 6 Mo<br>Restenosis ≥ 50% | 31% PTCA<br>16% Hepacoat PS Stent* | p = 0.0008 |
| STRESS | Lesion ≤ 15 mm<br>Vessel ≥ 3.0 mm | 410<br>31 (7.6) | 6 Mo Death, MI<br>or Revasc | 23.8% PTCA<br>19.5% PS Stent | p = 0.16 |
| | | 336 | 6 Mo<br>Restenosis ≥ 50% | 42.1% PTCA<br>31.6% PS Stent | p = 0.046 |
| START | Post PCI | 452<br>27 (6.0) | 4 Yr Death, MI<br>TVR | 29.9% PTCA<br>16.9% PS Stent | RR 0.57; [0.40, 0.81], p=0.0136 |
| | | | 6 Mo<br>Restenosis ≥ 50% | 37% PTCA<br>22% PS Stent | RR 0.60; [0.43, 0.82], p = 0.0013 |
| ISAR-SMART | Any Length<br>Vessel 2.0-2.8 mm | 404<br>100 (24.7) | 6 Mo Death, MI<br>Stroke or Revasc | 19% PTCA<br>23% Multi-Link Stent | p = 0.22 |
| | | | 6 Mo<br>> 50 % stenosis | 37.4% PCTA<br>35.7% Multi-Link Stent | p = 0.74 |
| STENT-PAMI | STEMI | 900<br>135 | 6 Mo Death, MI<br>Stroke or Ischemia-Driven TVR | 20.1% PTCA<br>12.6% PS Stent | p < 0.001 |
| OPUS | Lesion ≤ 20 mm<br>Vessel ≥ 3.0 mm | 479<br>87 (18.2) | 6 Mo Death, MI<br>or Revasc | 14.9% PTCA<br>6.1% BMS | HR 2.53; [1.38, 4.71] |
| RAVEL | Length < 18 mm<br>Vessel 2.5-3.5 mm | 238<br>45 *(19)* | 1 Yr Death, MI<br>or Revasc | 28.8% Bx Velocity stent<br>5.8% Cypher stent | RR 1.10 [0.93, 1.29] |
| | | | 6 Mo<br>>50% Stenosis | 26.6% Bx Velocity stent<br>0.0% Cypher stent | p < 0.001 |

*(Continued)*

Table 7
(Continued)

| *Trial* | *Population* | *N – Total N- DM (%)* | *Endpoint* | *Event Rates* | *Statistical Comparison* |
|---|---|---|---|---|---|
| SIRIUS | Length 15–30 mm<br>Vessel 2.5–3.5 | 1058 | 9 Mo Target Vessel Failure | 21.0% BxVelocity Stent<br>8.6% Cypher stent | RR 0.58, $p < 0.001$ |
| | | | 9 Mo > 50% Restenosis | 36.3% BxVelocity stent<br>8.9% Cypher stent | $p < 0.001$ |
| | | 279 (26.3) | 9 Mo Target Vessel Failure | 27.0% BxVelocity stent<br>12.2% Cypher stent | $p < 0.001$ |
| | | | 9 Mo >50% Restenosis | 50.5% BxVelocity stent<br>17.6% Cypher stent | $p < 0.001$ |
| E-SIRIUS | Length 15–32 mm<br>Vessel 2.5–3.0 mm | 352<br>81 (235) | 9 Mo Death, MI or Revasc | 22.6% BxVelocity stent<br>8.0% Cypher | Δ 14.6% [22.0, 7.2] $p = 0.0002$ |
| | | | 8 Mo >50% Restenosis | 42.3% BxVelocity stent<br>5.9% Cypher stent | Δ 36.4% [45.0, 27.8] $p = <0.0001$ |
| SISR | In Stent Restenosis | 384<br>123 (32.0) | 9 Mo Target Vessel Failure | 21.6% Brachytherapy<br>12.4% Cypher stent | RR 1.7 [1.1, 2.8], $p = 0.02$ |
| | | | 9 Mo > 50% Restenosis | 29.5% Brachytherapy<br>19.8% Cypher stent | RR 1.5 [1.0, 2.2], $p = 0.7$ |
| DIABETES | Any Length<br>Vessel < 4.0 mm<br>All Diabetic Subjects | 160 | 9 Mo Death, MI or Revasc | 36.3% Bx Velocity Stent<br>6.3% Cypher Stent | $p < 0.001$ |
| | | | 9 Mo >50% Restenosis | 33.7% Bx Velocity stent<br>7.8% Cypher stent | $p < 0.001$ |
| SES-SMART | Length < 33 mm<br>Vessel < 2.75 mm | 260 | 8 Mo Death, MI Stroke or Revasc | 31.3% Bx Velocity stent<br>9.3% Cypher stent | RR 0.20 [0.01, 0.93] $p = 0.04$ |
| | | | 8 Mo > 50% Restenosis | 53.1% Bx Velocity stent<br>9.8% Cypher stent | RR 0.18 [0.10, 0.32] $p < 0.001$ |
| | | 69 (26.5) | 8 Mo > 50% Restenosis | 63.4% Bx Velocity<br>25.0% Cypher stent | RR 0.19 [0.07, 0.56] |
| TAXUS IV | Length 10–28 mm<br>Vessel 2.5–3.75 mm | 1314 | 9 Mo Death, MI or Ischemia-Driven TVR | 15.0% Express stent<br>8.5% Taxus stent | RR 0.56 [0.41,0.77], $p < 0.001$ |
| | | | 9 Mo Ischemia-Driven TVR | 12.0% Express stent<br>4.7% Taxus stent | RR 0.39 [0.26, 0.59], $p < 0.001$ |
| | | | 9 Mo > 50% Restenosis | 26.6% Express stent<br>7.9% Taxus stent | RR 0.30 [0.19, 0.46] <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| | | 318 (24.2) | 1 Yr Death, MI or Ischemia-driven TVR | 27.7% Express stent<br>15.6% Taxus stent | RR 0.53 [0.32, 0.87] $p < 0.01$ |
| | | | 9 Mo > 50% Restenosis | 34.5% Express stent<br>6.4% Taxus stent | RRR 0.19 [0.07, 0.47] |
| TAXUS V | Length 10–46 mm<br>Vessel 2.25–4.0 mm<br>Complex Lesions | 1156<br>356 (30.8) | 9 Mo Death, MI or TVR | 21.2% Express Stent<br>15.0% Taxus Stent | RR 0.71 [0.55, 0.91] <0.008 |
| - | | | 9 Mo Ischemia Driven TVR | 17.3% Express stent<br>12.1% Taxus stent | RR 0.70 [053, 0.94] <0.02 |
| | | | 9 Mo >50% Restenosis | 33.9% Express stent<br>18.9% Taxus stent | RR 0.56 [0.45,0.69] $p < 0.001$ |
| TAXUS V ISR | In Stent Restenosis | 396<br>139 (35.1) | 9 Mo Death, MI or Revasc | 20.1% Brachytherapy<br>11.5% Taxus stent | RR 0.57 [0.35, 0.93] $p = 0.02$ |
| | | | 9 Mo Ischemia-Driven TLR | 17.5% Brachytherapy<br>10.5% Taxus stent | RR 0.60 [0.36, 1.00] $p = 0.046$ |
| TAXUS VI | Length 18–40 mm<br>Vessel 2.5–3.75 mm | 446<br>89 (20.0) | 9 Mo Death, MI or TVR | 22.5% Express2 stent<br>16.4% Taxus stent | $p = 0.12$ |
| | | | 9 Mo TVR*<br>9.4% Taxus stent | 19.4% Express2 stent | RR 0.53; $p = 0.0027$ |
| | | | 9 Mo Restenosis $\geq$ 50% | 32.9% Express2 stent<br>9.1% Taxus stent | $p < 0.0001$ |
| ISAR-DIABETES | Diabetic Subjects | 250 | 9 Mo TLR<br>6.4% Cypher stent | 12.0% Taxus stent | RR 1.89 [0.82, 4.27] $p = 0.13$. |
| | | | 9 Mo > 50% Stenosis | 16.5% Taxus stent<br>6.9% Cypher stent | RR 2.40 [1.04, 5.55] $p = 0.03$ |
| ISAR-SMART3 | Any Length<br>Vessel < 2.8 mm<br>Diabetes Excluded | 360<br>0 | 1 Yr Death or MI<br>5.0% Cypher stent | 5.6% Taxus stent | $p = 0.81$ |
| | | | 6 Mo >50% stenosis | 19.0% Taxus stent<br>11.4% Cypher stent | RR 1.67 [1.00, 2.79] |

*(Continued)*

**Table 7**
**(Continued)**

| *Trial* | *Population* | *N – Total*<br>*N- DM (%)* | *Endpoint* | *Event Rates* | *Statistical Comparison* |
|---|---|---|---|---|---|
| ISAR-DESIRE | In Stent Restenosis | 300 | 9 Mo TVR | 33.0% PTCA | |
| | | 83 (27.6) | | 19.0% Taxus stent | RR 0.58 [0.35, 0.94]* |
| | | | | 8.0% Cypher stent | RR 0.24 [0.12, 0.50]* |
| | | | 6 Mo | 44.6% PTCA | |
| | | | > 50% Restenosis | 21.7% Taxus stent | RR 0.49 [0.31, 0.76]* |
| | | | | 14.3% Cypher stent | RR 0.32 [0.18, 0.56]* |
| REALITY | Length >10 mm | 1386 | 1 Yr Death, MI | 11.4% Taxus | RR 0.94 [0.69, 1.27] |
| | Vessel 2.25–3.0 | 379 (27.3) | CABG or TLR | 10.7% Cypher | |
| | | | 8 Mo | 11.1% Taxus | RR 0.84 [0.61, 1.17] |
| | | | > 50% Restenosis | 9.6% Cypher | |

CAD: coronary artery disease
MI: myocardial infarction
CABG: coronary artery bypass surgery
PCI: percutaneous coronary intervention
PTCA percutaneous transluminal coronary angioplasty
RR: relative risk
RRR relative risk reduction
HR hazard ratio
TVR target vessel revascularization
BENESTENT BElgian NEtherlands Stent study
STRESS stent restenosis study
START Stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions
ISAR-SMART intracoronary stenting or angioplasty for restenosis reduction in small arteries
OPUS optimum percutaneous transluminal coronary angioplasty compared with routine stent strategy
RAVEL randomized study with the sirolimus-coated bx velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions
E-SIRUS European SIRolImUS-coated Bx Velocity balloon-expandable stent
SIRUS Sirolimus-Eluting Stent in de Novo Native Coronary Lesions
SISR Sirolimus-Eluting Stent for In-Stent Restenosis
DIABETES Diabetes and Sirolimus-Eluting Stent
SES-SMART Sirolimus-Eluting Stent in the Prevention of Restenosis in Small Coronary Arteries
ISAR-DIABETES The Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents
ISAR-SMART3 Intracoronary Drug-Eluting Stenting to Abrogate Restenosis in Small Arteries
ISAR-DESIRE Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis
REALITY Prospective, Randomized, Multi-Center Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems

inhibit neointimal hyperplasia. Two agents, rapamycin (sirolimus) and paclitaxel are currently in clinical use and have been applied to existing stent technology to create DES. The target of action of rapamycin is the target of rapamycim (TOR) protein (target of rapamycin), which arrests the mitotic cycle in the G1 phase following binding with rapamycin. The antiproliferative effects of rapamycin on vascular smooth muscle cells were soon appreciated, and during development as an agent to prevent in-stent restenosis it was subsequently renamed sirolimus. Currently, sirolimus is applied as a polymer matrix to a stainless steel stent and is marketed as the Cypher stent (Cordis Corporation, Miami Lakes, FL). The Cypher stent has been studied against conventional BMS in randomized controlled trials in simple and more complex PCI settings, and an overwhelming decrease in the incidence ISR has been found (Table 7) *(148–153)*. Among the patients with DM, the restenosis rates among uncomplicated lesions are similar to nondiabetic patients but, in small vessels and complicated lesions, diabetic patients continue to have increased risk of restenosis, despite utilization of the Cypher stent *(154,155)*.

An alternative DES utilizes paclitaxel as an antiproliferative agent. Paclitaxel was identified from the Pacific Yew tree and has been employed extensively as a chemotherapeutic agent. The mechanism of action is to interfere with microtubule function in the mitotic spindle leading to a subsequent arrest in M phase of mitosis. Currently it has been applied in a matrix that controls drug release over time to the Express stent (Boston Scientific Corporation, Natik, MA) and this DES is called the Taxus stent. Other stents are currently being designed using paclitaxel as well. Similar to the Cypher stent, initial studies with the Taxus stent have demonstrated a significant decrease in evidence of restenosis compared with BMS in a variety of PCI settings (Table 7) *(156–159)*. Advantages of the Taxus stent include its flexibility and deliverability compared with the Cypher stent owing to the characteristics of the stent and balloon platform.

**Drug Eluting Stents in Diabetic Patients.** Although the Taxus stent has demonstrated a clear clinical and angiographic benefit compared with BMS in diabetic patients, some head to head comparisons have favored the Cypher stent overall and in diabetic patients as well *(160–167)*. However, in the largest study, the Prospective, Randomized, Multi-Center Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems (REALITY) trial, no significant difference was found in the 8 mo restenosis rates or the cardiovascular event rates. (Table 7) *(168)*. In addition, given the mechanical characteristics and the technical challenges of delivering stents, the decision to implant a Cypher or Taxus stent may vary from case to case.

**Drug Eluting Stents and Late Stent Thrombosis.** A current topic of concern for DES implantation is an increased risk of late stent thrombosis, which has been reported as late as 14 mo after stent implantation *(169,170)*. Many coronary lesions are complex and involve bifurcation and small vessel disease, which have not been optimally studied in prospective trials, leading many to question the recommendations for duration of clopidogrel following DES implantation *(170,171)*. This concern is supported by observations in large registries, which have shown a small, but significantly increased risk of long-term mortality for patients with DES implantation compared with BMS implantation *(172)*. Although risk may be attenuated among patients treated with long term clopidogrel use, the optimal duration of clopidogrel use following DES implantation requires further study *(173)*, and the present recommendations are to use at least 12 mo of clopidogrel therapy following DES and always with concomitant aspirin therapy.

## CHOICE OF REVASCULARIZATION TECHNIQUE

With the development of PCI, controversy has arisen as to the appropriate modality of revascularization of patients with multivessel disease. Early studies of PCI with balloon angioplasty alone demonstrated a reduction in angina and a decreased risk of subsequent infarction in the target vessel, but in contrast to CABG, an impact on long term mortality was not established *(174)*. The Bypass versus Angioplasty Revascularization Investigation (BARI) was conducted to compare the 2 techniques and randomized 1829 patients with 2 vessel or 3-vessel CAD to CABG or balloon angioplasty *(175)*. Importantly, PCI did not include coronary stenting as the study started enrollment before formal approval of these devices. Patients eligible for the trial who declined randomization were also followed in a prospective registry. Overall, no significant difference in mortality or subsequent MI was appreciated among the patients randomized to CABG or surgery, but an increased risk of repeat revascularization was found in the patients randomized to PCI (Table 6).

However, analysis of the subgroup of diabetic patients demonstrated that PCI compared with CABG was associated with a clear reduction in long term survival in patients with both 2 and 3-vessel CAD *(176)*. In particular, this benefit among diabetic patients was associated with use of LIMA graft for the LAD and increased risk was noted among diabetic patients requiring insulin *(177)*. Interestingly, although this difference was not appreciated in the BARI registry, analyses from several other studies comparing bypass surgery and balloon angioplasty noted similar findings *(178–182)*. The explanation for this finding and its clinical implications has been extensively debated in the medical literature, and other trials have not been large enough to investigate the relationship between CABG and mortality in diabetic patients *(183)*. Subsequent analyses of the BARI data have demonstrated that diabetic patients tend to have diffuse disease and larger areas of potentially jeopardized myocardium that may not be adequately revascularized by percutaneous techniques. In addition, placement of a bypass graft in diabetic patients may protect against the consequences of future development of occlusive plaque or plaque rupture due to the accelerated course of atherosclerosis in DM. Based on the subgroup findings of BARI, revascularization with CABG has been recommended for diabetic patients with 2 or more vessel CAD.

One of the chief limitations of BARI is that it was conducted during the development of coronary stenting. During the course of the trial several randomized trials were published that clearly demonstrated a reduction in restenosis and stenting became more commonplace *(130,131)*. As a consequence, many clinicians have considered the BARI data to be outdated, even among the diabetic population. To evaluate the impact of coronary stenting compared with CABG, several studies have been conducted (Table 6). The Arterial Revascularization Therapies Study (ARTS) randomized patients with severe 2 vessel or 3-vessel disease to PCI with coronary stenting or CABG *(184,185)*. Similar to BARI, no overall significant difference was appreciated in long term risk of cardiovascular events, but PCI was associated with an increased risk of repeat revascularization. Although a mortality benefit was not appreciated in the diabetic patients, an increased risk of repeat revascularization was noted driven largely by an increased need for revascularization of the initial target vessel. In addition, the ARTS study was conducted largely with BMS, and also has been criticized as being outdated as the development of DES may have impacted on the rates of revascularization in diabetic patients *(186)*. Similar findings have been appreciated in other studies comparing various PCI techniques with bypass surgery (Table 6) *(187–207)*.

As a consequence, debate continues about the appropriate mode of revascularization for multivessel disease in diabetic patients. Although definitive data to guide revascularization in diabetic patients continues to be elusive, other clinical factors should be considered for revascularization of diabetic patients with multi-vessel or proximal LAD disease. Overall, the balance of the mortality evidence supports CABG as the preferred revascularization strategy for this high-risk cohort, but consideration should be given to the peri-operative risk of patients undergoing CABG. In ARTS, the mortality benefit of CABG among the diabetic subset was countered to a large extent by an increased risk of perioperative stroke. As a consequence, PCI is a reasonable alternative for patients with high peri-operative CABG risk such as the elderly or patients with cerebrovascular disease. In contrast, patients undergoing percutaneous intervention are likely to require repeat revascularization, which may be undesirable in some patients but may be acceptable in others. Selection of a revascularization strategy should account for the angiographic characteristics and extent of disease, patient age and comorbidities, and patient preference. Frequently, younger patients may agree to tolerate repeated percutaneous procedures in an attempt to delay bypass surgery, whereas older patients may be referred directly to surgery, as their operative risk from bypass grafting will increase with age. Currently, studies are ongoing to evaluate the role of DES and bypass surgery in revascularization of diabetic patients with multivessel disease, and completion of these studies may shed more insight into the appropriate approach to revascularization for individual patients.

## CONCLUSION

It is clear that optimal management of CAD in diabetic patients requires multiple therapeutic interventions, incorporating appropriate use of revascularization and a variety of lifestyle interventions and medical therapies. Analysis from prospective studies of DM has demonstrated that glucose management alone is not associated with a reduction in cardiovascular events (UKPDS) *(208,209)*. In contrast, utilization of multiple interventions, including antihypertensive therapy, hypoglycemic therapy, lipid lowering therapy and antiplatelet therapy has been associated with prevention of subsequent cardiovascular events. For example, the Steno 2 study found a reduction the hazard

of cardiovascular disease over a mean follow-up time of 7.8 yr among patients treated with an aggressive approach to glucose, lipid, and blood pressure control *(210)*. Importantly, patients undergoing revascularization procedures also benefit from aggressive risk factor modification. Observational studies have demonstrated that elevated hemoglobin A1c is an independent predictor of restenosis, target vessel revascularization, rehospitalization, and recurrent angina at 12 mo. Analyses from several clinical trials have clearly demonstrated the importance of intensive Glucose-lowering therapy following coronary revascularization. As a consequence the preponderance of evidence supports a comprehensive approach to management of CAD and other atherosclerotic diseases in diabetic patients, and frequently requires the concerted expertise of cardiovascular specialists, endocrinologists and the generalists for optimal and appropriate management.

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# 19 Peripheral Vascular Disease and Stroke in Type 2 Diabetes

*Robert G. Mitchell and Brian H. Annex*

***CONTENTS***



**Summary**

Peripheral arterial disease (PAD) is a common cardiovascular complication in patients with diabetes. The risk of developing PAD is much higher in patients with diabetes, and the disease is more severe and progresses more rapidly than in nondiabetic individuals. Moreover, the presence of PAD is a potent marker of increased cardiovascular risk. Because the major threat to patients with diabetes and PAD is from cardiovascular events, the primary therapeutic goal is to modify atherosclerotic risk factors. Risk factor management includes lifestyle modifications, treating associated conditions (diabetes, dyslipidemia, and hypertension), and preventing ischemic events with aggressive antiplatelet therapy such as clopidogrel. Revascularization has an important role in both extra-cranial carotid artery stenosis and symptomatic lower extremity atherosclerosis in the management of patients for whom risk factor modification and pharmacological treatment prove inadequate. The American Diabetes Association consensus statement strongly recommends that cardiologists act cooperatively and effectively with other clinical specialists to reduce the death and disability in patients with diabetes and PAD.

**Key Words:** Peripheral arterial disease (PAD); carotid stenosis; dyslipidemia; critical limb ischemia(CLI); ipsilateral stoke; antiplatelets; revascularization; intermittent claudication; type 2 diabetes.

## INTRODUCTION

Morbidity and mortality in patients with type 2 diabetes mellitus is most often owing to vascular disease *(1)*. Atherosclerosis and the associated arterial obstructive diseases account for 80% of mortality and over 70% of hospitalizations in patients with type 2 DM *(1)*. Although the 2 to 4-fold risk of coronary disease in diabetic patients is well recognized, the prevalence of cerebrovascular disease and peripheral arterial disease is vastly underappreciated. PAD affects 12 million individuals in the United States and is as common as coronary artery disease (CAD) *(2)*. Cerebrovascular disease is rapidly growing and affects 5 million Americans *(3)*. In both PAD and cerebrovascular disease, a disproportionate number of patients have type 2 DM *(4)*. Among patients with type 2 DM, 20–25% over the age of 45 have either cerebrovascular disease or PAD *(5)*.

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Atherosclerosis is a progressive disorder, which, if unchecked, leads to narrowing of arteries and ischemia to end organ tissues. The major vascular beds affected are the coronary circulation, the cerebrovascular bed, and the lower extremity arterial circulation. The major causes of vascular death directly parallel these focal vascular beds: myocardial infarction and heart failure, stroke, and critical limb ischemia. Type 2 diabetes is an independent risk factor for atherosclerosis *(6)*. Numerous epidemiological studies have confirmed a strong association between type 2 DM and CVD/PAD, implying a relationship between insulin resistance and associated metabolic abnormalities and much of the pro-atherosclerotic tendencies of the arteries, leading to increased cardiovascular disease *(4)*.

Cardiovascular care in the US has vastly improved over the last 3 decades, mostly owing to improved technologies and evidence based medicines designed to treat risk factors for vascular disease, leading to a marked decline in cardiovascular mortality over that past 2 decades *(7)*. Unfortunately, outcomes for diabetic patients have not improved and seem unlikely to do so in the near future *(8)*. The frequency of the metabolic syndrome continues to increase. Conservative estimates project 22 million cases of type 2 DM by 2025 *(8)*. This will cause an unprecedented drain on medical resources owing to poor cardiovascular outcomes.

This chapter will primarily focus on the prevalence, pathophysiology, diagnosis and treatment of cerebrovascular disease and peripheral arterial disease in patients with type 2 diabetes mellitus. A special emphasis will be given to evidenced based treatment decisions and how they can be implemented into everyday clinical practice.

## EPIDEMIOLOGY AND NATURAL HISTORY OF PERIPHERAL VASCULAR DISEASE IN PATIENTS WITH TYPE 2 DIABETES

### *Peripheral Arterial Disease*

Peripheral arterial disease (PAD) results from atherosclerosis that decreases perfusion to the lower extremities *(9)*. PAD is now recognized as a major health problem, currently affecting 8 to 12 million Americans *(2)*. As the incidence of diabetes continues to increase, prevalence of PAD will likely follow suit. The prevalence of PAD in nondiabetic patients is 6–9% by the age of 50 yrs and 20–25% after the age of 70. In diabetic patients, 21 % over the age of 50 have abnormal ankle brachial indices and PAD, and 45–61% over the age of 70 have PAD *(2)*. The duration of and severity of diabetes correlates with the extent of PAD. In the United Kingdom Prospective Diabetes Study (UKPDS), the data showed a higher prevalence of PAD in those with a longer duration of diabetes *(10)*. In addition every 1% increase in glycosylated hemoglobin confers a 28% increase in the risk of PAD *(10)*.

PAD is defined as infra-aortic arterial obstructive disease that leads to abnormal measures in lower extremity blood pressure and pulses. PAD is present as a spectrum of disease ranging from asymptomatic silent ischemia to critical limb ischemia leading to gangrene and amputation. The 2 major clinical manifestations of peripheral arterial disease of the lower extremity are intermittent claudication (IC) and critical limb ischemia (CLI) *(11)*. Patients with critical limb ischemia have a 25–40% risk of suffering either major amputation or death within 6 mo *(12)*. These events in patients with intermittent claudication occur at an annual rate of only 1–2% per year *(8)*. Although intermittent claudication is also a major health problem, patients with CLI experience substantially greater morbidity and mortality*(11)*, and there are no medical treatment options *(12)*.

Patients with type 2 DM more commonly present with symptomatic PAD manifested as intermittent claudication *(13)*. Nondiabetic patients with PAD only have classic claudication 30% of the time, as compared to diabetic patients with PAD who present with classic claudication 40–51 % of the time. *(8)*.Of those with IC, 20% will develop CLI, compared to only 4% in subjects without diabetes *(14)*. However, patients with type 2 diabetes may also present with CLI without warning and progress to limb amputation and death more quickly *(14)*. Faglia et al observed a positive correlation between PAD severity and amputation rates in patients with type 2 DM *(15)*. Patients with DM and CLI have 15 times the risk of amputation as nondiabetics without DM *(1)*.

### *Cerebrovascular Disease*

Among patients presenting with stroke the prevalence of DM is 3 times that of matched controls *(1)*. Similarly, patients with diabetes have a 3–4-fold increased risk of stroke *(1,16)* Diabetes increases the risk of stroke in younger patients (less than 55 yr of age ). Additionally, among patients with type 2 diabetes, African Americans and Hispanics have a 2-fold increase in stroke mortality compared to whites *(1)*. Finally, asymptomatic cerebrovascular

disease, defined as greater than 50% occlusion in atherosclerotic obstruction in the internal carotid arteries, is 5-fold greater in diabetic patients as assessed by carotid ultrasonagraphy than age matched nondiabetic patients *(17)*.

Stroke mortality and outcomes are also strongly influenced by the presence of diabetes. In the Renfrew-Paisley study, a 20 yr follow-up study of men and women aged 45–64 yr of age with stroke, diabetes raised the relative risk of death after stroke by 350% *(18)*

## PATHOPHYSIOLOGY

The pathophysiology of arterial obstructive disease in diabetic individuals is similar to that seen in nondiabetics. Although increased atherosclerotic burden is responsible for greater than 90% of cases of CVD and PAD in both diabetic patients and non diabetics, the distribution of disease in diabetic individuals more commonly affects the distal lower extremity tibial arteries in PAD rather than the more proximal aorto-illiac vessels *(8)*. In CVD, carotid disease prevails; however, diabetic patients have more small vessel disease in the inter-cranial vessels *(19)*.

The proatherogenic state seen in diabetes is thought to result from the metabolic abnormalities associated with insulin resistance and can be classified into 4 broad categories; 1) increased inflammation, 2) endothelial cell dysfunction, 3) increased vasoconstriction, and 4) increased platelet aggregation.

Inflammation is recognized as a main component in the development of atherosclerosis. C-reactive protein (CRP) is the current accepted marker for levels of inflammation. CRP levels are abnormally elevated in patients with type 2 DM, and CRP correlates positively with degree of atherosclerosis and cardiovascular event risk *(20)*. CRP has procoagulant effects related to tissue factor and also inhibits nitric oxide (NO) synthase, which increases vascular tone. CRP also potentiates clot formation by inhibiting plasminogen activator inhibitor-1.

Patients with type 2 diabetes exhibit profound endothelial dysfunction, which can be traced back to the individual endothelial cell *(21)*. The healthy endothelial cell plays an important role in platelet activation and smooth muscle cell migration. In patients with diabetes, endothelial production of NO is decreased, allowing smooth muscle cell proliferation and platelet aggregation to go unchecked, leading to increased vascular injury and subsequent atherosclerosis *(22)*.

Diabetic subjects have increased vascular tone and vascular smooth muscle migration owing to increases in vasoconstrictors, most notably endothelin-1 *(23)*. Smooth muscle migration, the process in which smooth muscles migrate from the tunica media to the tunica intima, is thought to play a critical role in progression to atheroma formation. Unlike atheromas in nondiabetic patients, the atheromas in diabetes are much more unstable owing to hyperglycemia induced lipid changes, increasing apoptosis in the plaque smooth muscle cells and leading to plaque rupture and cardiovascular events *(24)*.

Type 2 DM also leads to increased expression of glycoprotein Ib and IIb/IIIa receptors on platelets *(25)*. This causes increased thrombus potential and when atherosclerotic plaques do rupture platelets are more likely to aggregate and lead to more serious clinical events.

## DIAGNOSIS

### *Peripheral Arterial Disease*

Diagnosis of PAD identifies patients with type 2 DM at high risk for overall cardiovascular mortality. An asymptomatic diabetic patient with PAD has a 10-yr mortality of 45–51% *(8)*. Initiation of medical therapies to decrease overall cardiovascular risk is essential, and often the diagnosis of PAD is the earliest and easiest way to establish the presence of cardiovascular disease in diabetic patients.

The medical history and physical exam are important in determining the presence of PAD in diabetic patients. Duration of symptoms, presence of peripheral neuropathy, presence of ulcers, and venous disease often clarify the diagnosis and at other times cloud the ability to make a clinical diagnosis of PAD. A history of classic intermittent claudication, the presence of CAD, and a history of smoking almost always signal the presence of PAD *(14)*. The physical exam findings of femoral arterial bruits and absence of lower extremity pulses signifies a high likelihood of PAD; however, diabetic patients often have calcified arteries and retained pulses even in the presence of significant arterial occlusion. As such further diagnostic testing is essential to confirm the diagnosis.

The ankle brachial index (ABI) is the gold standard for detection of PAD and is 95% sensitive and 90% specific *(26)*. The ABI is defined as the ratio of the ankle systolic blood pressure to the brachial systolic blood pressure

and is normally between 1.00 and 1.30. In PAD, the ankle systolic blood pressure is less than the brachial systolic blood pressure, and the ABI is reduced to <1.00; PAD is defined as an ABI <0.90. Lower ABI values indicate more severe PAD and a higher risk of cardiovascular events. Type 2 diabetic patients with ABI's less than 0.40 have a 6-mo mortality of 40% *(12)*.

The risk of PAD is so high in patients with type 2 diabetes that the American Diabetes Association (ADA) consensus statement recommends that a screening ABI be performed in all diabetic individuals >50 yr of age. If normal (0.91–1.40), the test should be repeated every 5 yr. A screening ABI should be performed in any patient with symptoms of PAD. Ankle-brachial index determinations may be of limited value in some patients with diabetes, because calcification of the tibial arteries may render them noncompressible, resulting in unusually high ABI values (>1.40) *(1)*. Under these conditions, the ABI cannot distinguish patients who have arterial occlusion from those who do not, making the ABI unreliable. However, an elevated ABI is still predictive of an increased risk of cardiovascular events, and other noninvasive vascular tests should be considered to make the diagnosis of PAD. The algorithm to diagnose PAD in is outlined in Fig. 1.

In the patient with a confirmed PAD diagnosis in whom further investigation is required (usually in the context of planning a revascularization procedure), the next step is a vascular laboratory evaluation for segmental doppler pressure and pulse volume recordings. Segmental Doppler pressure volume recordings record blood pressure at various levels of the thigh and calf and can indirectly isolate the level of flow obstruction. Pulse volume recordings can further help the physician evaluate flow obstruction by recording the change of volume per each pulsation of the cardiac cycle through a particular limb segment. The waveforms are derived after attaching the blood pressure cuffs to a plethysmographic instrument, which records the pulse volume of blood. Both hemodynamic tests aid in the localization of arterial occlusive lesions. Other noninvasive imaging techniques, such as ultrasonic duplex scanning or magnetic resonance angiography (MRA), can be used when more precise measurements of the morphological features of occlusions are required (i.e., when considering various revascularization options). Ultrasonic duplex scanning can directly visualize vessels, providing information on artery wall thickness, degree of flow turbulence, and changes in blood flow velocity. Comprehensive imaging of the peripheral vasculature

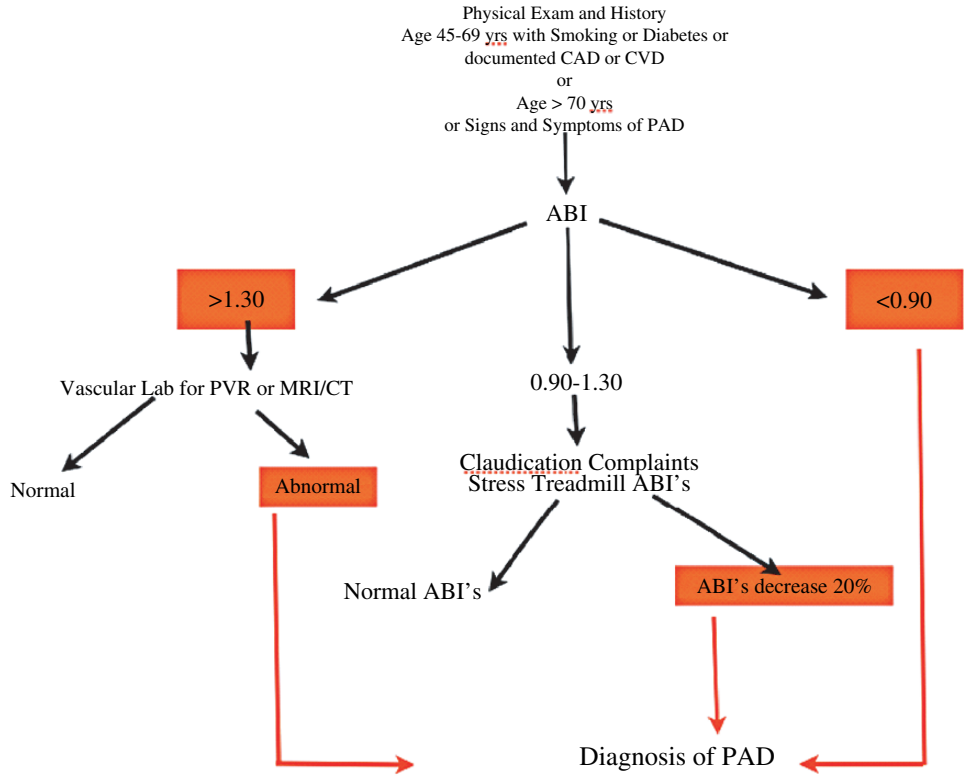


**Fig. 1.** Algorithm to diagnose PAD. Adopted from 2005 AHA/ACC guldelines on diagnostic work up for PAD.

has traditionally been possible only with invasive conventional angiography. However, with the introduction of MRA and computed tomographic angiography (CTA), noninvasive imaging is now a reality. Contrast-enhanced MRA produces images that are comparable to conventional angiography.

### *Cerebrovascular Disease*

The first presentation of cerebrovascular disease in patients with type 2 DM is often a debilitating stroke. A careful physical exam denoting the presence or absence of carotid pulse and bruits is often the clinician's first clue to the presence of cerebrovascular disease. A history of monocular blindness or transient ischemic attacks (TIAs) is highly suggestive of cerbrovascular disease and demands immediate attention and aggressive diagnostic testing. The presence of PAD or CAD in patients with type 2 DM also denotes a high probability of cerebrovascular disease and requires additional evaluation.

The screening diagnostic test of choice in evaluation of cerebrovascular disease is the carotid artery ultrasound. Stenosis greater than 50% is considered abnormal and is diagnostic of cerebrovascular disease*(7)*. The Adult Treatment Panel III guidelines identify greater than 50% internal carotid artery stenosis as a coronary heart disease equivalent *(13)*. Similar to PAD, more severe stenosis confers a greater risk of a cerebrovascular event, although no studies have been done solely in patients with diabetes. Depending on the degree of stenosis, further testing to determine the anatomic location and morphology of the stenosis can be useful when planning an interventional therapeutic approach. MRA and CTA give a much more detailed anatomic diagnosis and assist in tailoring medical and interventional therapies.

## MEDICAL THERAPY FOR PAD AND EXTRACRANIAL CAROTID ARTERY DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

The treatment of diabetes and the associated macrovascular complications of CAD, CVD, and PAD have evolved over the last decade to include a broad approach, focusing on reducing risk of the major factors associated with the development of cardiovascular disease. Control of hyperglycemia is just one component of care that now includes aggressive management of hypertension, dyslipidemia, thrombosis, and lifestyle. The presence of PAD or Cerebrovascular disease is a marker of systemic vascular disease, and the medical approach to both disease states involves reduction of cardiovascular risk.

### *Hyperglycemia and Insulin Resistance*

The treatment of hyperglycemia and insulin resistance is a fundamental component of the treatment of patients with type 2 DM. Glycoslylated hemoglobin levels over 6.2 % are associated with increased risk of all forms of macrovascular disease *(10)*. Despite this convincing epidemiologic data, 2 large trials did not show that intensive treatment of blood glucose reduces the risk of cardiovascular mortality. In both the Diabetes Control and Complications Study (DCCT) and the Veteran Affairs Study there was a trend in reduction of macrovascular events however neither study achieved statistical significance *(27)*. More recent data from the DCCT trial did show that intensive glycemic control slowed progression of intimal media thickness in the carotid artery of type 2 DM patients however hard stoke endpoint data will not be available until further follow up *(28)*.

The recent addition of thiazolidinediones to control hyperglycemia and insulin resistance provide the clinician with a new tool that directly reduces inflammation of the vascular endothelium *(29)*. However, there have been no studies of the effect of thiazolidinedione therapy on amputation or the development of peripheral vascular disease.

### *Treatment of Dyslipidemia*

The purpose of aggressively treating dyslipidemia in diabetic patients with CVD and PAD is to reduce the risk of cardiovascular mortality. To date all lipid-lowering trials that have included diabetic subjects have shown a reduction cardiovascular death with aggressive treatment of dyslipidemia *(30)*.

Elevated cholesterol levels are directly associated with increased risk of stroke, myocardial infarction, and the presence of PAD. The majority of trails have focused on the reduction of coronary events. The Heart Protection Study that randomized diabetic patients to high doses (40 mg once daily)of simvastatin reduced the risk of stroke and vascular interventions by 25% in diabetic patients *(31)*. The risk reduction even extended to patients with

pretreatment levels of LDL below 100mg/dL. Recent data from the Collaborative AtoRvastatin Diabetes Study (CARDS) validated aggressive primary prevention of cardiovascular events in patients with diabetes at risk for CAD, irrespective of pretreatment LDL cholesterol levels. In CARDS, patients treated with atorvastatin for a target LDL less than 70 mg/dL had a 37% risk reduction in the primary endpoint of first acute major cardiovascular event relative to placebo *(31)*.

### *Hypertension*

Hypertension increases the high risk of cardiovascular disease associated with diabetes. However, the role of intensive blood pressure control in patients with diabetes and PAD has not been established. The UKPDS showed that, although diabetes end points were significantly reduced by tight blood-pressure control, there was no effect on the risk of amputation owing to PAD *(10)*. Nevertheless, a marked reduction in vascular events with aggressive hypertension management has been demonstrated in diabetic individuals. The ADA consensus supports aggressive blood-pressure control (<130/80 mm Hg) in patients with diabetes and PAD to reduce cardiovascular risk. Studies, such as the Hypertension Optimal Treatment (HOT) trial and the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, have suggested that a lower target blood pressure may be beneficial *(32)*. The ABCD trial demonstrated improved outcomes (particularly nonfatal MI) for patients with PAD and diabetes who achieved a blood pressure of <125/75 mm Hg compared with 135/85 mm Hg *(18)*.

### *Antiplatelet Therapy*

In addition to the established risk factors, the risk of cardiovascular morbidity and mortality in PAD patients with diabetes also relates to platelet activity and inflammation. Platelet activity can be modified by the use of antiplatelet agents. The treatment goal is to prevent thrombus formation and the resultant vascular events.

A meta-analysis of 145 prospective, controlled trials of antiplatelet therapy (mainly aspirin) has been reported by the Antiplatelet Trialists' Collaboration. This analysis combined data from more than 100,000 patients, among them approx 70,000 high-risk patients with evidence of cardiovascular disease, including PAD. There was a 27% reduction in the odds ratio of the composite primary endpoint of MI, stroke, and vascular death for patients taking antiplatelet therapy compared with control subjects *(33)*. Aspirin has also been shown to significantly improve vascular graft patency in more than 3,000 patients with PAD treated with bypass surgery or peripheral angioplasty *(12)*. Aspirin at dosages of 80–162 mg/d is recommended by the American Diabetes Association for all diabetic individuals over 40 yr of age. Aspirin has an established role in secondary prevention in patients at high risk, with clinical evidence of either CAD or stroke. The role of aspirin in other populations, such as in patients with either PAD or diabetes, without clinical evidence of CAD or stroke, has not been established.

Clopidogrel, an adenosine diphosphate receptor antagonist, has potent antiplatelet activity. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study was the first to evaluate aspirin versus clopidogrel in patients with recent stroke, recent MI, or established PAD. The study compared clopidogrel at 75 mg/d with aspirin at 325 mg/d in more than 19,000 patients (approx 20% with diabetes). Patients treated with clopidogrel had an annual 5.32% risk of stroke, MI, or vascular death compared with a 5.83% risk in those treated with aspirin *(26)*. This represented a significant 8.7% relative-risk reduction in favor of clopidogrel ($p = 0.043$). In a subset analysis of 6,452 patients with PAD, clopidogrel recipients had a 23.8% relative-risk reduction compared with aspirin recipients ($p < 0.05$), with an annual event rate of 3.71% compared with 4.86% *(34)*. Furthermore, in the PAD subgroup, approximately one-third of the patients had diabetes; in these patients, clopidogrel was also superior to aspirin. On the basis of these results, clopidogrel was approved by the FDA for the reduction of ischemic events in patients with PAD. The ADA consensus recommends that patients with diabetes should be on an antiplatelet agent, and that those with PAD may benefit more by taking clopidogrel than aspirin. Despite the fact that DM leads to increases in expression of glycoprotein IIb/IIIa receptors on platelets, there are no current medical therapies to address this platelet abnormality in the chronic outpatient setting.

### *Intermittent Claudication*

The only proven medical treatments for intermittent claudication are supervised exercise therapy, and use of cilostazol, a phosphodiesterase inhibitor *(25)*. The best results with exercise therapy are achieved under

**Table 1**
**Recommended goals for risk factor modification**

| *Risk factor* | *Guideline goal* | *Grade of recommendation/level of evidence* | *Benefit* |
|---|---|---|---|
| Smoking | Abstinence | 1 Level A | Clear |
| Hyperglycemia | HgbA1c < 7% | IIa Level B | Likely Beneficial |
| Dyslipidemia | LDL < 100mg/dl | 1 Level A | Clear |
| Hypertension | BP < 130/80 | 1 Level A | Clear |
| Platelet Inhibition | Aspirin or clopidogrel | 1 Level A | Clear |

supervision, and should consist of daily walks with intermittent periods of rest and weekly increases in walking time and distance. Drug therapy can be added as adjunctive treatment to an exercise program, although this combination has not been well studied.

Cilostazol (Pletal) is probably the most effective agent available in the US. Cilostazol (100 mg twice daily) has been shown to improve maximal walking distance by 40% to 50% compared with placebo *(25)*. In a direct comparison, the mean maximal walking distance in PAD patients treated with cilostazol for 24 wk was significantly greater than that of patients who received pentoxifylline or placebo respectively *(25)*. Because of the potential increased risk of mortality, cilostazol is contraindicated if any degree of systolic or diastolic heart failure is present.

### *CLI*

Critical limb ischemia is owing to underlying severe ischemia. CLI is the precursor of limb loss and requires urgent treatment. Conservative management includes limited debridement of ulcers, the provision of appropriate footwear, use of nonadherent dressings, institution of adjunctive wound-healing techniques, and treatment of infection (unloading of the foot and administration of antibiotics). Surgical drainage and debridement are often required to resolve the infection, and revascularization is usually indicated. Revascularization is the only treatment for patients with CLI, as surgical debridement without revascularization tends to lead to larger nonhealing wounds.

## SURGICAL THERAPY OR ENDOVASCULAR INTERVENTION FOR PAD AND EXTRACRANIAL CAROTID ARTERY DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

### *Intermittent Claudication*

Many patients with intermittent claudication may not experience optimal improvement in symptoms with medical therapy alone. Revascularization has emerged as an important strategy for management of these patients. Two general revascularization techniques exist: endovascular interventions and open surgical procedures. Endovascular revascularization is more appropriate in patients with relatively focal disease in arteries above the knee; however, short-term success rates for opening long totally occluded vessels and below-the-knee arteries are improving. To date, the best results have been achieved in the aorto-iliac vessels, where 1-yr patency rates of 80–90% have been demonstrated and equal to the patency rates over 5 yr of surgical aorto-femoral bypass *(38)* For that reason endovascular treatment of aorto-illiac lesions are generally preferred at this time and are reflected in the PAD AHA/ACC 2005 guidelines as a Class I, level of evidence A, recommendation *(12,38)*. (Tables 2 and 3)

In diabetes, open surgical revascularization tends to have greater durability than endovascular procedures. Bypass to the tibial or pedal vessels with autologous vein is the most predictable method of improving blood flow to the threatened limb. Surgical bypass with greater saphenous vein is the procedure of choice for patients with diabetes and tibial disease *(35)*.

### *Critical Limb Ischemia*

Revascularization is the definitive therapy for the management of patients with CLI, with the aim of healing ischemic ulcers and preventing limb loss. Although most ischemic limbs can be revascularized, lack of a target

Table 2
Indications for Revascularization for Intermittent Claudication (Endovascular Approach)

| Recommendations |
|---|
| Class I |
| 1. Lifestyle limiting claudication with aorto-illiac obstuction |
| Level of Evidence A |
| 2. Lifestyle limiting claudication with stenoses less than 3 cm in iliac or femoro-popliteal arteries. |
| Level of Evidence B |
| Class IIa |
| 1. Stents or other adjunctive endovascular techniques in salvage therapy for suboptimal results from balloon dilatation of the femoral, popliteal, and tibial arteries. |
| Level of Evidence C |
| Class IIb |
| 1. Treatment of femoro-popliteal lesions by atherectomy, laser, thermal devices is not well established |
| Level of Evidence A |
| Class III |
| 1. Primary Stent placement in popliteal or tibial arteries. |
| Level of Evidence C |

Table 3
Indications for revascularization for intermittent claudication (surgical bypass)

| Recommendations |
|---|
| Class I |
| 1. Lifestyle limiting claudication with infra-ingunal disease |
| Level of Evidence A |
| 2. Lifestyle limiting claudication with aorto-illiac obstuction |
| Level of Evidence B |

vessel, unavailability of an autologous vein, or irreversible gangrene may mean that some cannot. In these patients, amputation may be a better option than prolonged medical treatment. The use of endovascular treatment for CLI is only indicated in inflow lesions (aorto-illiac) or femoro-poplieal lesions after inflow patency has been established(both are Class I, Level of B indications) Surgical Bypass is the treatment of choice for CLI patients and is a Class I, Level A recommendation *(38)*.

### *Revascularization of Extra-Cranial Carotid Stenosis*

Carotid endarterectomy is the gold standard treatment of choice for revascularization of the extra-cranial carotid artery stenosis *(36)*. In symptomatic patients, and for asymptomatic patients with greater than a 80% stenosis, the benefit of CEA outweighs the risk of stroke *(37)*. Recently, carotid artery stenting has emerged as an alternative and several recent trials found that it is not inferior to CEA *(36)*. Currently it is only FDA approved in surgically high-risk patients with symptomatic stenosis or high-grade asymptomatic stenosis *(36)*.

### *Symptomatic Carotid Artery Stenosis*

All patients with symptoms related to severe carotid stenosis fare better with carotid endarterectomy than with medical care alone. In the absence of life-threatening disease they should undergo the procedure. Symptomatic patients with the conditions listed in Table 4 face a much greater risk of stroke when treated medically than those without these conditions. Therefore, carotid endarterectomy is recommended for the patients shown in Table 4. Many, but not all, patients with moderate stenosis who are symptomatic benefit from carotid endarterectomy. For such patients the benefit is much smaller than for patients with severe stenosis. Tables 4 and 5 show that patients with moderate stenosis who show benefit from surgical intervention.

**Table 4**
**Patients who benefit from carotid endarterectomy with symptomatic severe stenosis of the internal carotid artery (> 70%)**

- Otherwise healthy elderly patients (75 yr or older)
- Patients presenting with hemispheric transient ischemic attack
- Patients with tandem extra cranial and intracranial lesions
- Patients without angiographic evidence of collateral pathways.
- Occlusion of the contralateral carotid artery
- Intraluminal thrombus.

**Table 5**
**Patients who benefit from carotid endarterectomy with symptomatic moderate stenosis (50% to 69%) of the internal carotid artery**

- Patients with transient monocular blindness only, especially those with few risk factors
- Women with few risk factors.

## *Asymptomatic Carotid Stenosis*

Carotid endarterectomy for subjects with an asymptomatic, less than 80% stenosed carotid artery has marginal benefit and questionable safety, and the decision to proceed is dependent on the surgical mortality *(37)*. For patients with less than 3% surgical mortality and greater than 5 yr' life expectancy, it is acceptable to perform CEA on asymptomatic patients with greater that 60% stenosis *(37)*. Careful attention by the physician to choose which individual patient will benefit from the procedure is vital. Carotid artery stenting is likely to expand the indications for revascularizing lower grade carotid stenosis, but large trials need to evaluate this important question. The best management for subjects with asymptomatic carotid stenosis is to treat hypertension, diabetes

**Table 6**
**For asymptomatic patients with a surgical risk of 3% and life expectancy of at least 5 yr.**

***Proven indications:*** Ipsilateral carotid endarterectomy is acceptable for stenotic lesions (>60% diameter reduction of distal outflow tract with or without ulceration and with or without antiplatelet therapy, irrespective of contralateral artery status, ranging from no disease to occlusion.

***Acceptable indications:*** Unilateral carotid endarterectomy simultaneous with coronary artery bypass graft for stenotic lesions (60% with or without ulcerations with or without antiplatelet therapy irrespective of contralateral artery status)

***Uncertain indications:*** Unilateral carotid endarterectomy for stenosis of 50% with ulcer irrespective of contralateral internal carotid artery status

**Table 7**
**For asymptomatic patients with a surgical risk of 3% to 5% and life expectancy of at least 5 yr.**

***Proven indications:*** None

***Acceptable but not proven indications:*** ipsilateral carotid endarterectomy for stenosis 75% with or without ulceration but in the presence of contralateral internal carotid artery stenosis ranging from 75% to total occlusion

***Uncertain indications:***

a) Ipsilateral carotid endarterectomy for stenosis >75% with or without ulceration irrespective of contralateral artery status, ranging from no stenosis to occlusion

b) Coronary bypass graft required, with bilateral asymptomatic stenosis >70%, unilateral carotid endarterectomy with coronary artery bypass graft (CABG)

c) Unilateral carotid stenosis >70%, CABG required, ipsilateral carotid endarterectomy with CABG

mellitus, and hyperlipidemia, to encourage smoking cessation, to administer prophylactic therapy with aspirin, and to monitor for the development of treatable cardiac conditions. Committees from the American Heart Association (AHA) and the National Stroke Association have endorsed the recommendations in Tables 4 through 7 *(36)*.

## CONCLUSIONS

Peripheral arterial disease is a common cardiovascular complication in patients with diabetes. The risk of developing PAD is much higher in patients with diabetes, and the disease is more severe and rapidly progressive than in nondiabetic individuals. Moreover, the presence of PAD is a potent marker of increased cardiovascular risk. Because the major threat to patients with diabetes and PAD is from cardiovascular events, the primary therapeutic goal is to modify atherosclerotic risk factors. Risk factor management includes lifestyle modifications, treatment of associated conditions (diabetes, dyslipidemia, and hypertension), and prevention of ischemic events with aggressive antiplatelet therapy such as clopidogrel. Revascularization has an important role in both extracranial carotid artery stenosis and symptomatic lower extremity atherosclerosis in the management of patients for whom risk factor modification and pharmacological treatment prove inadequate. The ADA consensus statement strongly recommends a cooperative approach to treatment to reduce the death and disability in patients with diabetes and PAD.

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# 20 Obesity and Its Treatment in Type 2 Diabetes

*Frank L. Greenway and William T. Cefalu*

***CONTENTS***



**Summary**

The prevalence of obesity began rising about 1980, and one third of the US population is now obese. The medical risks of obesity are linked to insulin resistance, and diabetes prevalence follows that of obesity by a decade. This chapter approaches the treatment of obesity in the context of diabetes. The role of behavior modification, meal replacements and commercial weight loss programs are discussed. Medications that were approved before 1986 are approved for short-term use and are chemically related to amphetamine. Obesity medications approved after 1986 and are approved for long-term use, and include a lipase inhibitor and an inhibitor of norepinephrine and serotonin reuptake. All these drugs give modest weight losses of less than 5kg in excess of placebo. Rimonabant, a cannabanoid-1 receptor antagonist received an approvable letter from the FDA for the treatment of obesity, but its new drug application was ultimately rejected. Metformin and acarbose are 2 oral diabetes medications that give some degree of weight loss, as do the injectable diabetes medications, pramlintide and exenatide. Thiazoladinediones, sulfonylureas and insulin give weigh gain whereas the meglitinides and the DPP-4 inhibitors are weight neutral. Restrictive surgical procedures like the lap-band are one type of obesity surgery, and restrictive-malabsorptive procedures like gastric bypass is the other. Weight loss is more durable and the improvement in diabetes is more dramatic with the restrictive-malabsorptive procedures. Lifestyle change is the basis for all obesity treatments. Obesity medications and surgical procedures are useful adjuncts and all obesity treatments are best delivered by a team, as is the case with diabetes.

**Key Words:** Behavior modification; gastric bypass; lap-band; orlistat; rimonabant; sibutramine.

## INTRODUCTION

In very simple terms, obesity can be defined as an excessive amount of body fat, which increases the risk of medical illness and premature death, and obesity develops over time when an individual consumes more calories than he/she burns. In this regard, obesity can be viewed as developing secondary to an imbalance in energy balance. In general, the concept of an energy balance equation implies that food consumption, i.e., "*energy intake,"* needs to match energy output*, i.e., "energy expenditure,"* to maintain a stable body weight. As well described, the major determinants of energy expenditure are: 1) the thermogenic effect of food (TEF), which represents the amount of energy used by ingestion and digestion of food we consume; 2) physical activity; and 3) resting metabolic rate (RMR), determined in large measure by the amount of lean body mass. As research over the recent past has shown, however, obesity is not such a simple process, as insight into the mechanisms that contribute to its development have revealed systems that are complex and highly integrated. Over the recent past, as key regulators

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of energy balance and insulin signaling have been elucidated, there has been a rapid and substantive increase in our understanding of underlying physiologic systems and molecular pathways that contribute to the development of obesity. Although it is recognized that there have been many changes in our environment that promote obesity, it is also clear that many individuals manage to resist obesity. Thus, there appears to be evidence that the variable susceptibility to obesity in response to environmental factors is undoubtedly modulated by specific genes *(1,2)*. It has also been determined that there is a dynamic interplay between adipose tissue and other key tissues in the body, such as liver, muscle and regulatory centers of the brain. Altered regulation of this integrated and coordinated system inevitably leads to accumulation of body fat, insulin resistance and development of associated cardiovasular risk factors.

Clinically, assessments such as body weight and body mass index (BMI) have been used for years to define obesity. As well described, the BMI assessment represents the relationship between weight and height and is derived by: 1) calculating either the weight (in kg) and dividing by the height (in meters squared), or; 2) calculating weight (in pounds) times 704 divided by height in inches squared *(3)*. The importance of the BMI assessment is that it allows classification of obesity into specific risk categories (Table 1). Such a risk classification is based on data collected from large population based studies that assessed the relationship between body weight and mortality and provides the clinician a mechanism for identifying patients at high risk for complications associated with obesity *(4,5)*.

Although the body weight and BMI have served an important purpose in stratifying individuals at high risk, the assessment of the specific distribution of the body fat, e.g., central or abdominal obesity, has been suggested as an even more important assessment. In past studies, body fat distribution has been generally assessed by anthropometric measurements consisting of waist circumference, the waist/hip ratio (WHR), or skinfold thickness. Subsequently, more sophisticated techniques such as computed tomography (CT) scans or magnetic resonance imaging (MRI) scans have been used to assess central obesity. These techniques allow for the specific and precise quantification of abdominal fat depots. Using such methods, the relationship among specific adipose tissue depots, e.g., visceral fat depots, to peripheral muscle insulin sensitivity and other metabolic risk factors can be assessed.

The prevalence of obesity has reached epidemic proportions around the world and the rate continues to increase; it is estimated that over 1 billion adults worldwide are overweight and at least 300 million are considered obese. There is no question that major contributors to this epidemic across the world include sedentary lifestyles, consumption of high fat, caloric-dense diets, and increased urbanization. Data from the National Health and Nutrition Examination Surveys in the United States have shown a dramatic shift in the percentage of the population considered overweight and obese. The most recent data demonstrate that 64% of the US adult population is classified as either overweight or obese (defined as BMI > 25). Whereas the prevalence of overweight adults increased slightly from data collected in 1960, from approx. 30.5% to 34.0 %, the prevalence of obesity (defined as a BMI $\geq$ 30) has more than doubled, rising from approx. 13% in 1960 to over 30% in the year 2000 *(6)*. The prevalence of individuals with extreme obesity, as defined by a BMI $\geq$ 40, has changed even more dramatically, increasing over 6-fold in the 40-yr period (0.8% versus 4.7%). Thus, there are tremendous economic, medical and psycho-social consequences of this obesity epidemic, which will need to be addressed.

**Table 1**
**BMI associated disease risk**

| | *Obesity class* | *BMI (kg/m$^2$)* | *Risk* |
|---|---|---|---|
| Underweight | | <18.5 | Increased |
| Normal | | 18.5–24 9 | Normal |
| Overweight | | 25.0–29 9 | Increased |
| Obesity | I | 30.0–34 9 | High |
| | II | 35.0–39 9 | Very high |
| Extreme obesity | III | $\geq$40 | Extremely high |

Additional risks: (1)waist circumference >40 inches in men and >35 inches in women;
(2) weight gain of$\geq$5 kg since age 18–20 (3) poor aerobic fitness; and
(4) Southeast Asian descent

**Table 2**
**Medical complications associated with obesity**

| | |
|---|---|
| Gastrointestinal | Gallstones, pancreatitis, abdominal hernia, NAFLD (steatosis, steatohepatitis, and cirrhosis), and possible GERD |
| Endocrine/metabolic | Metabolic syndrome, insulin resistance, imparied glucose tolerance, type 2 diabetes mellitus, dyslipidemia, polycystic ovary syndrome |
| Cardiovascular | Hypertension, coronary heart disease, congestive heart failure, dysrhythmias, pulmonary hypertension, ischemic stroke, venous stasis, deep vein thrombosis, pulmonary embolus |
| Respiratory | Abnormal pulmonary function, obstructive sleep apnea, obesity hypoventilation syndrome |
| Musculoskeletal | Osteoarthritis, gout, low back pain |
| Gyneocologic | Abnormal menses, infertility |
| Genitourinary | Urinary stress incontinence |
| Ophthalmologic | Cataracts |
| Neurologic | Idiopathic intracranial hypertension (pseudotumor cerebri) |
| Cancer | Esophagus, colon, gallbladder, prostate, breast, uterus, cervix, kidney |
| Postoperative events | Atelectasis, pneumonia, deep vein thrombosis, pulmonary embolus |

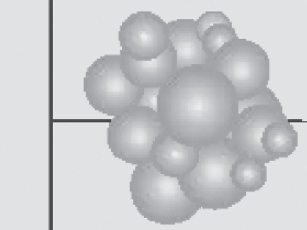
* Adapted from reference 3.

The major concern associated with the obesity epidemic is the expected increase in prevalence of the associated complications, which seem to affect every major organ system, and particularly the increase in cardiovascular risk factors (Table 2). Obesity has been suggested to increase an individual's risk for cancer, gastrointestinal diseases, arthritis, diabetes, and cardiovascular disease. Specifically, obesity is significantly associated with both the traditional risk factors (i.e., hypertension, dyslipidemia, and diabetes) and the nontraditional Risk factors (i.e., fibrinogen and inflammatory markers) of cardiovascular disease. Furthermore, if one considers the presence of insulin resistance as the hallmark of the cardio-metabolic risk syndrome, it is clear that obesity and insulin resistance are integrally related.

In addition to the significance of the relationship of obesity to medical complications, there is new understanding from research studies that adipose tissue is not merely a passive reservoir for energy storage, but is a very active endocrine organ. Specifically, adipose tissue has been shown to express and secrete a number of bioactive proteins referred to as adipocytokines in addition to expressing numerous receptors that allow it to respond to different

**Table 3**
**Adipocyte derived Proteins and receptor**

| Adipocyte-derived proteins | Receptors expressed in adipose tissue |
|---|---|
| Leptin | Insulin receptor |
| Tumor necrosis factor-α (TNF-α) | Glucagon receptor |
| Interleukin-6 (IL-6) | Growth hormone (GH) receptor |
| Monocyte chemoattractant protein-1 (MCP-1) | Thyroid stimulating hormone (TSH) receptor |
| Plasminogen activator inhibitor-1 (PAI-1) | Gastrin/cholecystokinin BN (CCK-B) receptor |
| Tissue factor | Glucagon like peptide-1 receptor |
| Adipsin (complement factor D) | Angiotensin II receptors type 1 and 2 |
| Complement factor B | Glucocorticoid receptor |
| Acylation stimulating protein (ASP) | Vitamin D receptor |
| Adiponectin | Thyroid hormone receptor |
| Lipoprotein lipase (LPL) | Androgen receptor |
| Cholesterol ester transfer protein (CETP) | Estrogen receptor |
| Apolipoprotein E | Progesterone receptor |
| Non-esterified fatty acids (NEFAs) | Leptin receptor |
| Cytochrome P450-dependent aromatase | Interleukin-6 (IL-6) receptor |
| 17β-hydroxysteriod dehydrogenase | Tumor necrosis factor-α (TNF-α) receptor |
| 11β-hydroxysteriod dehydrogenase-1 | β1, β2, β3 receptors |
| Angiotensin (AGT) | α1, α2 receptors |
| Resistin | |



Adapted from reference 7

Table 4
Levels of evidence for diabetes prevention

| *Recommendation* | *Level of evidence (reference #)* |
|---|---|
| Lifestyle intervention causes weight loss of 5-10% and reduces the incidence of diabetes in people with impaired glucose tolerance | 1A *(10)* |
| Calorie controlled portions are an important dietary tool to aid in a weight loss program | 1-B *(13)* |
| Commercial weight loss programs like Weight Watchers and Jenny Craig give a clinically significant weight loss that is greater than self-help weight loss | 1A *(14,18)* |
| Sibutramine causes a mean weight loss of less than 5kg in excess of placebo in diabetic subjects | 1A *(27)* |
| Orlistat causes a mean weight loss of less than 5 kg in excess of placebo in diabetic subjects | 1A *(30)* |
| Orlistat and sibutramine give statistically similar weight losses in diabetic subjects | 1B *(32)* |
| Rimonabant causes weight loss similar to sibutramine, but gives greater improvements in insulin resistance | 1A *(43)* |
| Metformin gives a weight loss of approx 2 kg and reduces the risk of converting from impaired glucose tolerance to type II diabetes | 1A *(10)* |
| Pramlintide use in diabetic subjects is associated with weight loss | 1A *(47)* |
| Exenatide use in diabetic subjects is associated with weight loss | 1A *(54)* |
| Acarbose use in diabetic subjects is associated with a small weight loss | 1A *(56)* |
| Restrictive surgical procedures for weight loss like the lap-band regain about half the lost weight between 1 and 10 yr postoperatively | 1C |
| Restrictive-malabsorptive surgical procedures for weight loss cause a greater improvement in diabetes than purely restrictive procedures | 1C |

hormonal signals (Table 3 ). Thus, in addition to its function to store and release energy, adipose tissue is able to metabolically communicate with other organ systems, and, in this way, contributes greatly to biological processes that include energy metabolism, neuroendocrine and immune function.

## PHARMACOLOGIC AND SURGICAL TREATMENT

The treatment of obesity and diabetes share common ground beyond the fact that the 2 diseases often coexist in the same patient. Both diabetes and obesity are chronic diseases for which a team approach is required if treatment is to be optimally safe and effective. The medical treatment of obesity with pharmaceuticals should be accompanied by a lifestyle program to be optimally effective, and the surgical treatment of obesity should employ a team approach involving medical and surgical disciplines to deliver treatment with optimal safety. The need for a team approach presents a challenge, which the presence of diabetes may make both easier and harder to surmount. On one hand, weight loss is more difficult and more complicated in the presence of diabetes. However, third party reimbursement for obesity treatment is better in the presence of diabetes, and monetary resources often determine the treatments that it is possible to deliver.

In discussing the pharmacologic and surgical treatment of obesity in the diabetic patient, we will discuss the role of behavior modification or lifestyle change programs and strategies to deliver them in the context of a diabetes practice. We will discuss the medications approved for the treatment of obesity and the most efficient manner to employ them. We will also discuss the impact of diabetes medications on body weight. Finally, we will discuss the role of obesity surgery in the treatment of diabetes, the reasons for the greater efficacy of restrictive-malabsorptive procedures, and the health care team needed to deliver surgical treatment of obesity with optimal safety.

## BEHAVIOR MODIFICATION AND LIFESTYLE CHANGE

A major challenge to the delivery of a lifestyle change program is the lack of preparation and lack of interest of most physicians in providing behavior modification to their patients. The argument has been made that the physician, by virtue of his or her authority, is the most appropriate person to advise the patient on behavior changes that can result in weight loss. The medical treatment paradigm, however, is not designed to allow time for this activity and an argument can be offered that doing so would violate the law of comparative advantage.

Physicians usually see patients every 15 min, and diabetic subjects often have multiple medical problems to be addressed in that short period of time. It is, therefore, not surprising that the typical physician's advice consists of telling patients who need to lose weight that their diabetes would improve with weight loss and increased physical activity. If patients are to get the behavior modification and lifestyle counseling they need, a referral is generally required. The insulin requiring diabetic patient in poor control represents a special challenge, but it is a challenge that most third party payers are prepared to address. The team effort of a diabetic educator, dietitian, and physician working together can address the needs for a lifestyle change program while, at the same time, addressing the challenges of dietary regulation and glycemic control. Obesity treatment alone is more problematic, because it is often not covered by third party payers, leaving patients to seek out lifestyle change programs on their own.

Behavior modification results in loss of approx 10% of initial body weight over 16–26 wk *(8)*. A 5-10% loss of initial body weight has been demonstrated to produce clinically important benefits *(9)*. Continued contact with the therapist can help maintain the major proportion of that weight loss. In the Diabetes Prevention Program, subjects in the lifestyle change program lost an initial 7% of body weight and at 3 yr maintained a 4% body weight loss accompanied by a 58% reduction in the conversion from impaired glucose tolerance to diabetes *(10)*.

Weight loss in patients with diabetes represents a particular challenge. Patients with diabetes lose approximately half the weight of nondiabetic patients *(11)*. Because newly diagnosed diabetic patients seem to lose as much weight as nondiabetic individuals, the reduced weight loss in diabetic patients may be owing to chronic dietary restraint related to physicians admonishing diabetic patients to lose weight *(12)*. Regardless of the reason, diabetic subjects, who have greater medical reasons to lose weight, do so at a reduced rate compared to their nondiabetic counterparts.

### *Diabetes Education and Dietitian Counseling*

As previously mentioned, many third party payers will cover behavior modification and weight loss for patients with diabetes through diabetic education programs and coverage for dietitian consultations. As the diabetes becomes less difficult to manage and is controlled with diet or oral agents, the likelihood of third party coverage for lifestyle programs to induce weight loss diminishes. Because physicians do not have the time or inclination to administer lifestyle counseling themselves, other methods to deliver a lifestyle modification program must be sought. This usually means some type of commercial weight loss program.

### *Calorie-Controlled Portions*

Calorie-controlled portions like SlimFast® once or twice daily have been compared to diets of comparable caloric content that use an exchange system. A 1-yr long study compared a group taking 2 meal replacements per day for 3 mo followed by 1 meal replacement/d with a group following an exchange diet of similar calories for 3 mo followed by 1 meal replacement daily. The group starting with meal replacements lost 11.3 ± 6.8% of initial body weight at 1 yr compared to the group initially using an exchange diet, which lost 5.9 ± 5.0% *(13)*. Thus, calorie-controlled portions can be a powerful tool in delivering a weight loss program (Fig. 1).

### *Commercial Weight Loss Programs*

Weight Watcher's is a commercial program that delivers a lifestyle change program using counselors who are successful graduates of the program. The program uses a balanced diet constructed from food lists, is conducted in a group context and is relatively inexpensive. A 6-mo controlled trial comparing Weight Watcher's to a self-help

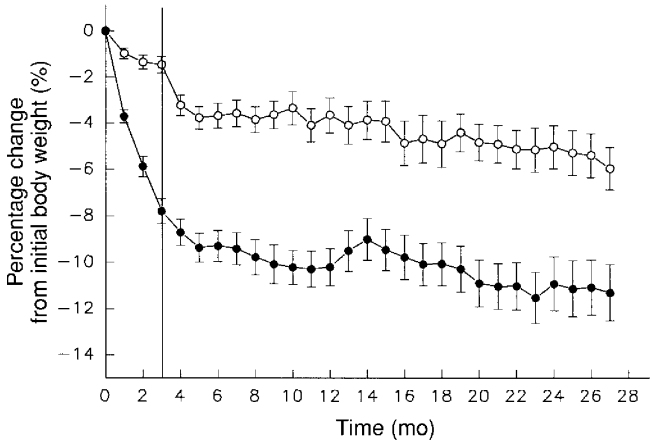



**Fig. 1.** Mean (± SEM) percentage change from initial body weight in obese patients during 27 mo of treatment with an energy-restricted diet containing 5.2-6.3 MJ/d. Data were analyzed on an available case basis. During the first 3 mo (phase 1), patients were randomly assigned to receive the energy-restricted diet only (group A, ○) or to receive the energy-restricted diet with 2 meals and 2 snacks replaced by energy-controlled, nutrient-dense meal-replacement products (group B, ●). During the next 24 mo (phase 2), all patients received the energy-restricted diet and 1 meal and 1 snack were replaced by energy-controlled, nutrient-dense meal-replacements products. Am J Clin Nutrition 1999;69:198–204.

weight loss group resulted in a 4.8 ± 5.6 kg weight loss in the Weight Watcher's group compared to a 1.4 ± 4.7 kg weight loss in the self-help group *(14)*. This weight loss was greater than 5% of initial body weight and clinically significant. At 2 yr, subjects in the Weight Watcher's group maintained more than a 3% weight loss while weight in the self-help group returned to baseline *(15)*.

A recent review of commercial weight loss programs concluded that the only well controlled trial was the study of the Weight Watcher's program, but called for "naturalistic studies" of program results *(16)*. The Jenny Craig program, which combines calorie-controlled portions with individual behavior and lifestyle counseling, recently published such a study of their program *(17)* (Fig. 1). Those subjects who remained in the program for a year lost 15.6 ± 7.5% of their initial body weight. Rock et al published a 1 year study comparing the Jenny Craig program with a self-help control group *(18)*. The Jenny Craig group lost 7.8 ± 11.1 of initial body weight compared to 0.7 ± 6.2% in the control group (Fig. 2). The Jenny Craig program is more expensive than the Weight Watcher's program, in addition to being more effective. These studies give the physician some basis upon which to make a referral to a commercial weight loss program.

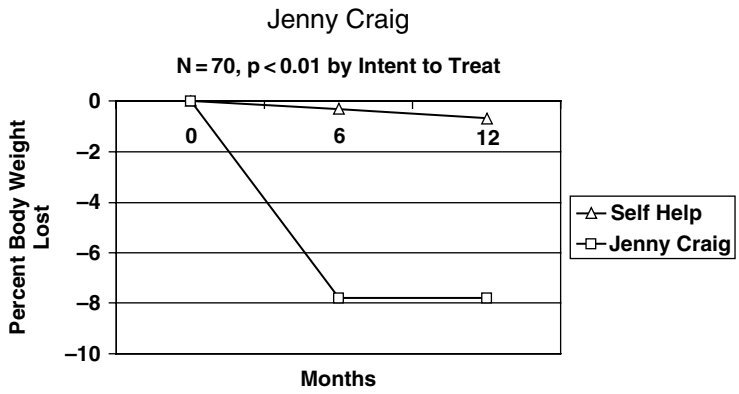



**Fig. 2.** A randomized study comparing the Jenny Craig program to self-help weight loss. The Jenny Craig group lost significantly more weight at 6 and 12 months than the self-help group (ref *18*).

## PHARMACOLOGIC TREATMENT

There are 2 medications presently approved for the long-term treatment of obesity, sibutramine and orlistat. Medications approved before 1985, the year the NIH conference declared that obesity is a chronic disease, were approved and tested for up to 12 wk as an adjunct to diet and lifestyle change *(19)*. There is one medication, remonabant, which was issued an approvable letter for long-term weight loss by the Food and Drug Administration (FDA) but the New Drug Application (NDA) was rejected by the Food and Drug Administration due to concerns of depression, anxiety and neurological adverse events. Rimonabant is approved in Europe and some other countries throughout the world for the treatment of obesity. Medicines used to treat diabetes can have an impact on body weight in both directions but most diabetes drugs cause weight gain. We will review drugs approved for the treatment of obesity and describe rimonabant, since it is approved in countries outside the United States.

### *Obesity Medication Approved for Short-Term Use*

Drugs approved before 1985 for the treatment of obesity are chemically related to amphetamine, and all are associated with some degree of CNS stimulation. Phentermine and diethylpropion are in DEA class IV and are felt to have a lower abuse potential than phendimetrazine and benzphetamine (class III) or phenmetrazine (class II). One might logically ask if these drugs can be useful in a chronic disease when they are all approved for up to 12 wk of use. There is a study comparing phentermine given continuously to phentermine given every other month and to a placebo in a 36-wk trial *(20)*. The intermittent use of phentermine gave equivalent weight loss to continuous use. The intermittent regimen gave lower drug exposure, was less expensive and allowed phentermine to be used in a way that is consistent with its package insert. Although the long-term studies of these drugs are limited, phentermine gave a 7.9 kg greater weight loss than placebo in a 1-yr trial *(21)* (Fig 3).

### *Sibutramine*

Sibutramine is a reuptake inhibitor of norepinephrine and serotonin. Its use results in 2.8 kg more weight loss than a placebo at 3 mo and 4.5 kg more weight loss than placebo at 1 yr *(22)*. The adverse events associated with the use of sibutramine are associated with its adrenergic mechanism of action and include dry mouth, insomnia, and nausea. Sibutramine treatment is associated with the improvement in glucose and lipids expected with weight loss. However, sibutramine use is associated with an average increase in pulse rate of 4 beats per min, and the expected improvement in blood pressure is not seen, probably owing to noradrenergic stimulation.

In a 6-mo dose-ranging study of 1,047 patients, there was a clear dose-response effect, and patients regained weight when the drug was stopped *(23)*. In a trial in patients who initially lost weight eating a very-low-calorie diet

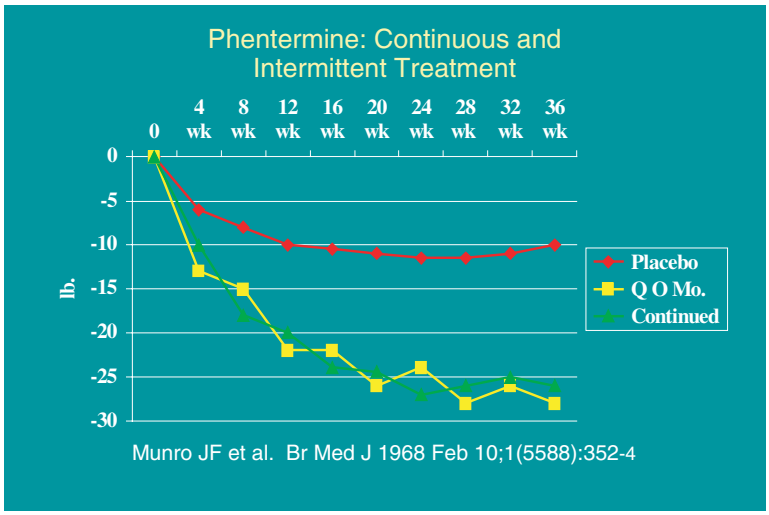



**Fig. 3.** Intermittent treatment versus continuous phentermine.

before being randomized to sibutramine (10 mg/d) or placebo, sibutramine produced additional weight loss, while the placebo-treated patients regained weight *(24)* The Sibutramine Trial of Obesity Reduction and Maintenance lasted 2 yr and provided evidence for weight maintenance *(25)*. Patients were initially enrolled in an open-label phase and treated with 10 mg/d of sibutramine for 6 mo. Of the patients who lost more than 8 kg, two-thirds were then randomized to sibutramine and one-third to placebo. During the 18-mo double-blind phase of this trial, the placebo-treated patients steadily regained weight, maintaining only 20% of their initial weight loss at the end of the trial. In contrast, the subjects treated with sibutramine maintained their weight for 12 mo and then regained an average of only 2 kg, thus maintaining 80% of their initial weight loss after 2 yr *(26)*. Despite the higher weight loss with sibutramine at the end of the 18 mo of controlled observation, the blood pressure levels of the sibutramine-treated patients were still higher than in the patients treated with placebo.

Studies with diabetic patients treated with sibutramine have also been published. In one such trial, sibutramine 20 mg/d was studied in 175 subjects with poorly controlled diabetes. The sibutramine group lost 4.5% of initial body weight compared to 0.5% in the placebo group. Fasting insulin, glycemic control, triglycerides, HDL cholesterol, and quality-of-life assessment improved commensurate with the weight loss, but blood pressure and pulse increased except in those that lost more than 5% of initial body weight *(27)*.

Sibutramine is available in 5-, 10-, and 15-mg doses; 10 mg/d as a single dose is the recommended starting level, with titration up or down depending on the response. Doses higher than 15 mg/d are not recommended. Of the patients who lost 2 kg (4 lb) in the first 4 wk of treatment, 60% achieved a weight loss of more than 5%, compared with less than 10% of those who did not lose 2 kg (4 lb) in 4 wk. Combined data from 11 studies of sibutramine showed a reduction in triglyceride, total cholesterol, LDL cholesterol levels and an increase in HDL cholesterol levels that were related to the magnitude of the weight loss.

### *Orlistat*

Orlistat is an inhibitor of pancreatic lipase and causes one-third of dietary fat to be lost in the stool *(27)*. Orlistat is designed for use with a 30% fat diet. Its use is associated with approx 3.2 kg more weight loss than placebo at 6 mo and 3.2 kg more weight loss than placebo at 1 yr *(28)*. The adverse events associated with the use of orlistat can be predicted from its mechanism of action. There is an increased incidence of diarrhea, flatulence and dyspepsia. Orlistat use results in the expected decrease in blood glucose and blood pressure with weight loss, but gives a reduction in lipids in excess of that expected for the degree of weight loss, probably because it enforces a low-fat diet. Orlistat is available in 120 mg doses; and 120 mg 3 times per day with meals is the recommended dose. An over-the-counter dose of 60 mg 3 times a day is expected to be available shortly.

Orlistat has also been studied in diabetic patients. In a 1-yr study of 391 subjects taking a sulfonylurea, the orlistat group lost 6.2 ± 0.45% of initial body weight compared to 4.3 $\pm$ 0.49% in the placebo group, and diabetic control improved to a greater degree in the orlistat group commensurate with the weight loss *(29)*. A 4-yr trial randomized 3,305 subjects, 79% with normal glucose tolerance and 21% with impaired glucose tolerance to orlistat 120 mg 3 times a day or a placebo. At the end of 4 yr, 52% remained in the orlistat group compared to 34% in the placebo group. The orlistat patients not only lost more weight, 3.6 kg versus 1.4 kg, but the conversion to diabetes was reduced by one-third, to 6.2%, in the orlistat group, compared to 9% in the placebo group *(30)*.

### *Comparing and Combining Orlistat and Sibutramine*

Orlistat and sibutramine were compared in a double-blind randomized clinical trial of 113 subjects over 1 yr . Both medications induced significant weight loss, but there was no statistically significant difference among them *(31)*. A similar trial in 144 type 2 diabetic subjects confirmed these results *(32)*.

Because orlistat and sibutramine work by different mechanisms, it is logical to ask whether using them in combination might give additive weight loss. The first trial addressing this question treated subjects with sibutramine for 1 yr and added orlistat during weight maintenance. No further weight was lost by the addition of orlistat *(33)*. Three studies compared sibutamine, orlistat and the combination. The first trial of 80 subjects showed more weight loss in the combination and sibutramine 10 mg/d groups than either the orlistat 120 mg 3 times per day or the diet alone groups, but the sibutramine group and the combination group did not differ from each other *(34)*. This finding was confirmed by a second study using a similar design *(35)*. The third trial compared orlistat 120 mg 3 times daily to sibutramine 10 mg/d and the combination in 89 obese subjects. The sibutramine and the

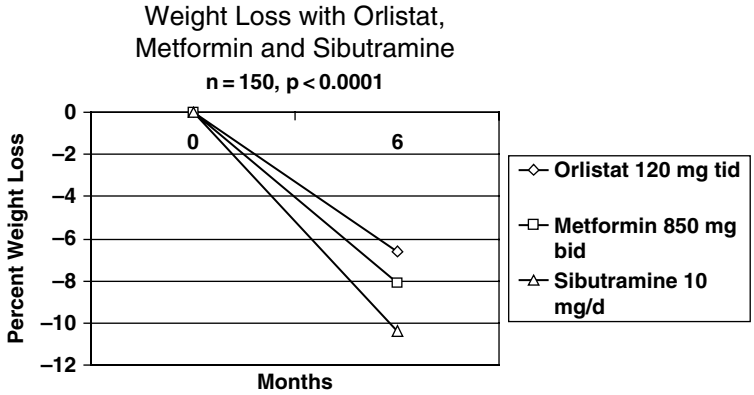



**Fig. 4.** Sibutramine, metformin, and orlistat in diabetes.

combination groups lost 10.2% and 10.6 % of initial body weight, respectively, which was not different but was greater than the 5.5% weight loss in the orlistat group *(36)*. A trial in obese type 2 diabetic subjects compared metformin 850 mg twice per day to sibutramine 10 mg twice per day and orlistat 120 mg 3 times per day. The sibutramine group lost more weight (10.4%) than the orlistat group (6.6%) or the metformin group (8.1%) *(37)*. In summary, sibutramine use appears to result in superior weight loss and is better tolerated than orlistat, but orlistat use is associated with the expected decrease in blood pressure not seen with sibutramine (Fig. 4).

### *Combining Sibutramine with Behavior Therapy*

Although there does not seem to be an advantage of combining sibutramine and orlistat, advantage of combining sibutramine with behavior therapy has been well demonstrated. In one study, 224 subjects were randomized to 4 groups: 1) Sibutramine 15 mg/d, delivered by a primary care provider in 8 visits of 10–15 min each, 2) Lifestyle-modification counseling alone, delivered in 30 group sessions, 3) Sibutramine plus 30 group sessions of lifestyle-modification counseling (i.e., combined therapy), 4) Sibutramine plus brief lifestyle-modification counseling, delivered by a primary care provider in 8 visits of 10–15 min each. At 1 yr , subjects who received combined therapy lost a mean 12.1 kg, subjects using sibutramine alone lost 5.0 kg, the lifestyle modification alone group lost 6.7 kg, and those receiving sibutramine plus brief therapy lost 7.5 kg *(38)* (Fig. 5) (subjects who received combined therapy ost significantly more weight at all times than subjects in the other three groups. Subjects treated with lifestyle modification alone and those treated with sibutramine plus brief therapy lost significantly more weight at week 18 than those who received sibutramine alone, with no other significant differences at any other time. Panel B shows that a last-observation-carried-forward analysis yielded the same statistical conclusions). The importance of lifestyle modification has been demonstrated in diabetic subjects as well. Obese type 2 diabetic subjects were randomized to a standard lifestyle program or a combination program using calorie-controlled portions and sibutramine, in addition to the lifestyle change program. At 1 yr , the lifestyle group lost 0.8 kg compared to 7.3 kg in the combined group and the combined group had statistically better glycemic control *(39)* (Fig. 5).

### *Rimonabant*

Rimonabant is approved for the treatment of obesity in Europe and some other countries, but although it received an approvable letter from the FDA, its approval was denied by the United States Food and Drug Administration due to safety concerns about depression, anxiety and neurological adverse events. The mechanism by which rimonabant causes weight loss is thought to be through inhibition of the cannabinoid-1 receptor. There are 2 cannabinoid receptors, CB-1 (470 amino acids in length) and CB-2 (360 amino acids in length). The CB-1 receptor has almost all the amino acids that comprise the CB-2 receptor and additional amino acids at both ends. CB-1 receptors are distributed throughout the brain in the areas related to feeding, on fat cells, in the gastrointestinal tract and on immune cells. Marijuana and tetrahydrocannabinol stimulate the CB-1 receptor,

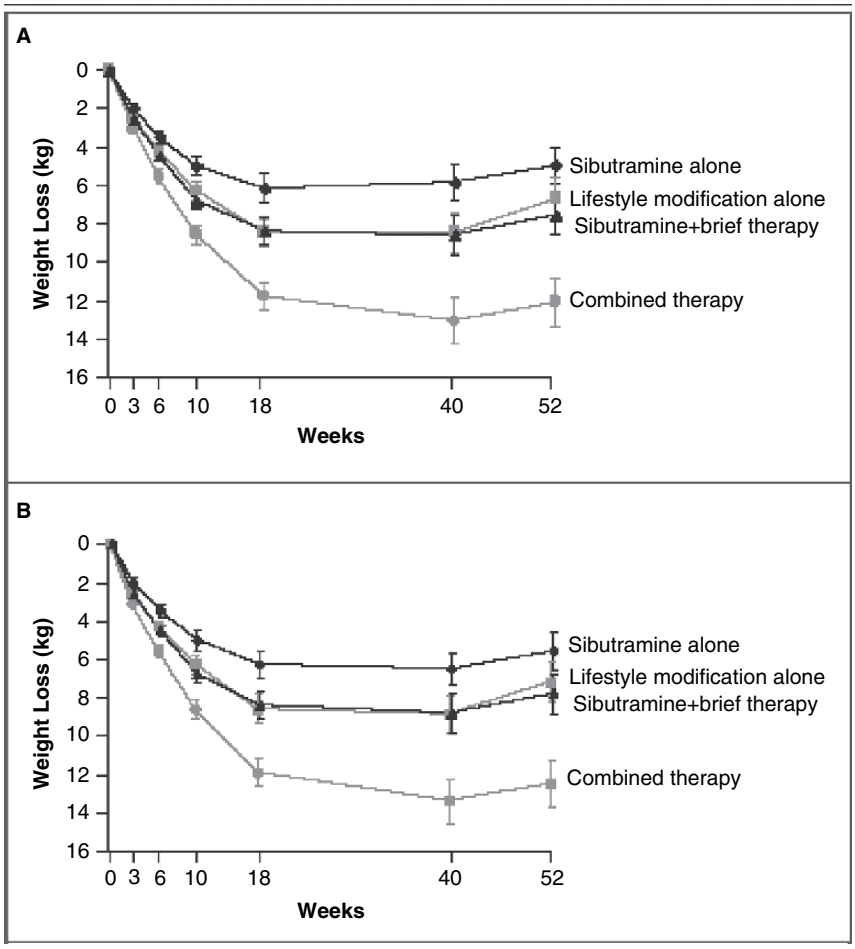



**Fig. 5.** Mean (±SE) weight loss in the 4 groups as determined by an intention-to-treat analysis (panel A) and a last-observation-carried-forward analysis (panel B). Subjects who received combined therapy lost significantly more weight at all times than subjects in the other three groups. Subjects treated with lifestyle modification alone and those treated with sibutramine plus brief therapy lost significantly more weight at week 18 than those who received sibutramine alone, with no other significant differences at any other time. Panel B shows that a last-observation-carried-forward analysis yielded the same statistical conclusions. (From Wadden et al. NEJM 353: 20, 2005).

increase high-fat and high-sweet food intake, and increase fasting levels of endocannabinoids such as anandamide and 2-arachidonyl-glycerol. The rewarding properties of cannabinoid agonists are mediated through the meso-limbic dopaminergic system. Rimonabant, being a specific antagonist of the CB-1 receptor, inhibits sweet food intake in marmosets as well as high-fat food intake in rats, but not food intake in rats fed standard chow. In addition to being specific in inhibiting highly palatable food intake, pair feeding experiments in diet-induced obese rats show that the rimonabant treated animals lost 21% of their body weight compared to 14% in the pair-fed controls. This suggests, at least in rodents, that rimonabant increases energy expenditure in addition to reducing food intake. CB-1 knockout mice are lean and resistant to diet-induced obesity, but have an accelerated cognitive decline with aging *(40)*. CB-1 receptors are up-regulated on adipocytes in diet-induced obese mice, and rimonabant increases adiponectin, a fat cell hormone associated with insulin sensitivity *(41)*.

The results of 3 phase III trials of rimonabant for the treatment of obesity have been published. The first trial to be announced was called the Rio-Lipids trial. This was a 1-yr trial that randomized 1,018 obese subjects equally to placebo, rimonabant 5 mg/d, or rimonabant 20 mg/d. The subjects in this trial had untreated dyslipidemia, a BMI between 27 and 40 kg/m$^2$ and a mean weight of 96kg. Weight loss was 2% in the placebo group and 8.5% in the 20 mg rimonabant group. In the 20 mg/d rimonabant group, waist circumference was reduced 9cm, triglycerides

were reduced by 15% and HDL cholesterol was increased by 23% compared to 3.5 cm, 3% and 12%, respectively, in the placebo group. In addition, in the 20-mg group, LDL particle size increased, adiponectin increased, glucose decreased, insulin decreased, C-reactive protein decreased and the metabolic syndrome prevalence was reduced by half. Although blood pressure did not increase, the expected improvement with weight loss was not seen. Fifteen percent of subjects in the rimonabant 20-mg group dropped from the trial for adverse events. The most common reasons for discontinuation were anxiety, depression and nausea, as one might expect from the location of the CB-1 receptors *(42)*.

In the second 1-yr study called Rio-Europe, 305 subjects were randomized to placebo, 603 subjects to rimonabant 5 mg per day and 599 subjects to rimonabant 20 mg/d. Weight loss at 1 yr in the placebo group was 1.8 kg compared to 7.2 kg in the 20-mg rimonabant group, and triglycerides, HDL cholesterol, waist circumference, insulin resistance and the metabolic syndrome all improved *(43)*. The third study, Rio-North America, was a 2-yr study that randomized 3,045 obese subjects without diabetes to placebo, 5 mg rimonabant or 20 mg rimonabant. At 1 yr, half the rimonabant groups were re-randomized to placebo. At 1 yr only 55% of the rimonabant 20-mg group remained in the trial. Weight loss was 1.6 kg in the placebo group and 6.3 kg in the 20-mg rimonabant group. At 2 yr there was weight regain in those rerandomized to placebo and weight maintenance in those re-randomized to continued rimonabant *(44)*.

## DIABETES MEDICATIONS

There are a wide variety of diabetes medications available. Some decrease weight to a modest extent, others are neutral, and some, including insulin, increase body weight. Thus, the choice of diabetes medications can play an important role in whether obesity improves or worsens. If possible, medications that cause weight loss while improving glycemic control should be considered first in the obese type 2 diabetic subject.

### *Metformin*

Metformin is a biguanide that reduces hepatic glucose production, decreases intestinal glucose absorption and enhances insulin sensitivity. In clinical trials where metformin was compared with sulfonylureas, it produced weight loss *(45)*. In one French trial, BIGPRO, metformin was compared to placebo in a 1-yr multi-center study of 324 middle-aged subjects with upper body obesity and the insulin resistance syndrome (metabolic syndrome). Subjects on metformin lost significantly more weight (1–2 kg) than the placebo group, and the study concluded that metformin may have a role in the primary prevention of Type 2 diabetes *(46)*.

The best trial of metformin, however, is the Diabetes Prevention Program, which enrolled individuals with impaired glucose tolerance. Subjects were over 25 yr of age and overweight, with impaired glucose tolerance. They were randomized to lifestyle ($N$ = 1,079), metformin ($N$ = 1,073) or usual care (N=1082). At the end of 2.8 yr, on average, the trial was terminated because lifestyle and metformin were clearly superior to usual care. During this time, the metformin-treated group lost 2.5% of their body weight ($p < 0.001$ compared to usual care), and the conversion to diabetes was reduced by 31% compared to placebo. Metformin was most effective in reducing conversion to diabetes in those who were younger and more overweight *(10)*. Although metformin does not produce enough weight loss (5%) to qualify as a "weight-loss drug" using the FDA criteria, it would appear to be a very useful choice for overweight individuals with diabetes or those at high risk for diabetes.

### *Pramlintide*

Amylin is secreted from the beta cell along with insulin, and amylin is deficient in type 1 diabetes where beta cells are immunologically destroyed. Pramlintide, a synthetic amylin analog, is approved by the FDA for the treatment of diabetes. Unlike insulin, pramlintide is associated with weight loss. Maggs et al analyzed the data from two 1-yr studies in insulin treated type 2 diabetic subjects randomized to pramlintide 120 mcg twice daily or 150 mcg 3 times daily *(47)*. Weight decreased by 2.6 kg and hemoglobin A1c decreased 0.5%. When weight loss was analyzed by ethnic group, African Americans lost 4 kg, Caucasians lost 2.4 kg, Hispanics lost 2.3 kg, and the improvement in diabetes correlated with the weight loss, suggesting that pramlintide is more effective in an ethnic group with the greatest obesity burden. The most common adverse event was nausea, which was

usually mild and confined to the first 4 wk of therapy. Thus, pramlintide should be considered in insulin treated patients with obesity and type 2 diabetes.

### *Exenatide*

Exendin-4 (exenatide) is a 39-amino-acid peptide that is produced in the salivary gland of the Gila monster lizard and has been approved for the treatment of type 2 diabetes. It has 53% homology with GLP-1 but has a much longer half-life. Exenatide decreases food intake and body weight gain in Zucker rats while lowering HbA1c *(48)*, inducing satiety and weight loss with peripheral administration and crossing the blood brain barrier to act in the central nervous system *(49,50)*. Exenatide increases beta-cell mass to a greater extent than would be expected for the degree of insulin resistance *(51)*. In humans, exenatide reduces fasting and postprandial glucose levels, slows gastric emptying and decreases food intake by 19% *(52)*. The side effects of exenatide in humans are headache, nausea and vomiting that are lessened by gradual dose escalation *(53)*. Exenatide at 10 mcg subcutaneously per day or a placebo was given for 30 wk to 377 type 2 diabetic subjects who were failing maximal sulfonylurea therapy. In the exenatide group, the HbA1c fell 0.74% more than placebo, fasting glucose decreased and there was a progressive weight loss of 1.6kg *(54)*. In ongoing open-label clinical trials, the weight loss at 18 mo is –4.5 kg without using behavior therapy or diet and –5.3 kg at 3 years (55).

### *Acarbose*

Acarbose, an alpha glucosidase inhibitor that is approved for the treatment of diabetes, has been evaluated for weight loss in a 9-mo trial randomizing 354 obese type 2 diabetic subjects to acarbose or placebo. The placebo group gained 0.3 kg while the acarbose group lost 0.5 kg (56). Although this is a small weight loss, it was statistically significant, and even the lack of weight gain can be a victory in treating the obese type 2 diabetic individual.

### *DPP-4 Inhibitors*

Sitagliptin, an inhibitor of DPP-4, is a recently approved class of medications for the treatment of diabetes, and there are other DPP-4 inhibitors in development. DPP-4 is the enzyme that breaks down the incretin hormones from the gut, like glucagon-like peptide-1 (GLP-1). Clinical trials with sitagliptin show it to be weight neutral and to decrease glycohemoglobin by approximately 1% *(57)*

### *Diabetes Drugs Causing Weight Gain*

Although the meglitinides seem to be weight neutral, sulfonylurea medication gives an average 0.42 kg weight gain per year and insulin therapy gives an average 0.44 kg per year weight gain *(58)*. Thiazolidinediones are the most problematic diabetes drugs in terms of weight gain. Subjects gained an average of 15–20 pounds over 3 yr of treatment that tended to plateau in subsequent years *(59)*. Thus, this drug class presents the greatest challenge to the obese type 2 diabetic patient needing to lose weight, despite its recognized efficacy in improving glycemic control.

## OBESITY SURGERY

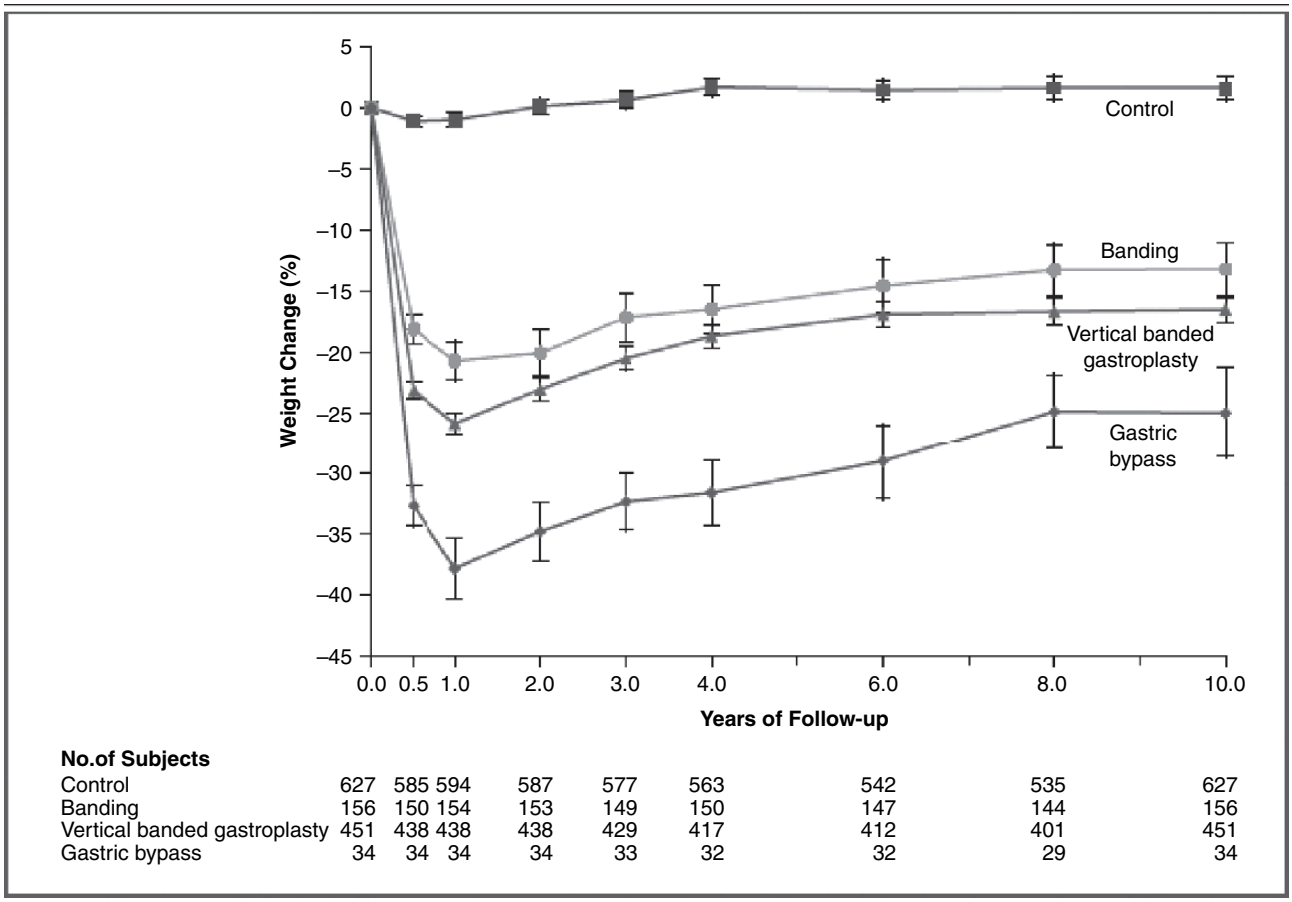
As reviewed earlier in this chapter, behavior modification yields an approximate 10% weight loss, with similar results from obesity drugs. Medical weight loss programs rarely last more than 2 yr, and weight maintenance results have been disappointing. The prevalence of class III obesity, a BMI >40kg/m$^2$ and the degree of obesity that would qualify for obesity surgery, increased from 0.5% in 1995 to 7.5% in 2002 in African-American women alone *(60)*. Individuals with class III obesity cannot, with rare exceptions, lose and keep off the weight needed to achieve a healthy body weight with medical interventions. It is in that context that those with class III obesity are turning in greater numbers to obesity surgery.

Surgical procedures have evolved since the 1950‘s, when the first operative attempts to treat obesity were performed. The present surgical procedures in common use can be divided into those that restrict the stomach, represented most commonly by the lap-band, and those that both restrict the stomach and have a malabsorptive component, represented most commonly by the gastric bypass. Although there are other restrictive procedures such as vertical gastric banding and other restrictive-malabsorptive procedures such as biliopancreatic bypass with

and without a duodenal switch, one can generalize the discussion to these 2 classes of surgical procedures. Thus, this chapter will discuss these 2 classes of surgical procedures separately and comment on the greater efficacy of restrictive-malabsorptive procedures in preventing and reversing type 2 diabetes.

### *Restrictive Procedures*

The lap-band, a restrictive procedure, is the preferred operation in most of Europe owing to its minimal distortion of the normal gastrointestinal anatomy and its ease of reversal. Despite these advantages, the weight loss with this procedure is less (20–25% versus 30–35% of initial body weight) and the need for surgical revision is higher (10% versus 5%) than restrictive-malabsorptive procedures like the gastric bypass *(61)*. The improvement in diabetes and other obesity associated diseases following restrictive procedures is proportional to the weight loss. The Swedish Obese Study consisted mostly of restrictive procedures. Weight loss in the lap band group was 20–25% at 1 yr postoperatively but only 10–15% at 10 yr. Only 9 (47%) of the 19 subjects with diabetes had resolution of their diabetes following the lap band placement. The incidence of developing diabetes at 10 yr was 7% in the surgical group and 24% in the medically treated control group *(62)*. These incidence rate reductions appear to be related to the weight loss, in contradistinction to the restrictive-malabsorptive procedures, in which the incidence reduction in diabetes is greater than can be attributed to weight loss alone *(63)* (Fig. 6)




| No.of Subjects | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Control | 627 | 585 | 594 | 587 | 577 | 563 | 542 | 535 | 627 |
| Banding | 156 | 150 | 154 | 153 | 149 | 150 | 147 | 144 | 156 |
| Vertical banded gastroplasty | 451 | 438 | 438 | 438 | 429 | 417 | 412 | 401 | 451 |
| Gastric bypass | 34 | 34 | 34 | 34 | 33 | 32 | 32 | 29 | 34 |

**Fig. 6.** Weight changes among subjects in the SOS study over a 10-yr period. All data are for subjects who completed 10 yrs of the study. The average weight change in the entire group of surgically treated subjects was almost identical to that in the subgroup of subjects who underwent vertical banded gastroplasty. The I bars represent the 95 percent confidence intervals (Graph from SOS study NEJM with lap bond).

### *Restrictive-Malabsorptive Procedures*

These surgical procedures cause food to bypass the upper gastrointestinal tract, reaching the distal small intestine earlier and in a less digested state. This causes a decrease in the release of hormones from the upper gastrointestinal tract, such as ghrelin, a hormone that initiates feeding. This decrease in upper gastrointestinal hormones is not associated with medical weight loss *(64)*. Hormones such as PYY-3-36 from the distal gut are increased after gastric bypass: PYY-3-36 has been shown to decrease food intake by 30–35% after intravenous infusion *(65,66)*. Thus, PYY-3-36 may be partly responsible for the more efficient weight loss seen after bypass operations compared to purely restrictive procedures. Glucagon-like peptide-1 (GLP-1), another distal gut hormone that increases after gastric bypass may be partly responsible for the enhanced effect that bypass operations have on reducing the prevalence of diabetes *(67)*. GLP-1 inhibits pancreatic glucagon secretion stimulates insulin secretion *(68)*, and increases beta-cell mass *(69)*. GLP-1 only stimulates insulin secretion at high glucose levels, so it is not associated with hypoglycemia.. Exenatide, a GLP-1 analog, stimulates the GLP-1 receptor and is a treatment for diabetes that causes weight loss, as described earlier in this chapter.

Possibly due, in part, to the effects of gastric bypass on gut hormones, the gastric bypass is much more efficient in reversing diabetes. Pories et al and Hickey et al reported a 14-yr experience with gastric bypass surgery patients, with an extraordinary 97% follow-up, in which 121 (82.9%) of the 146 patients with type 2 diabetes and 150 (99%) of the 152 patients with IGT completely normalized their glucose metabolism *(70,71)* (Fig. 7). In a comparison study of morbidly obese patients undergoing gastric bypass and morbidly obese controls, Long et al showed the gastric bypass imparted a greater than 30-fold decrease in the risk of developing type 2 diabetes after weight loss *(72)*.

The return to euglycemia, however, is rapid and is observed within 10 d postoperatively following gastric bypass, before any significant weight loss occurs *(70,71,73)*. Therefore, the reduction of food intake may be playing an additional role. Scopinaro et al observed that serum glucose levels normalized in patients with preoperative type

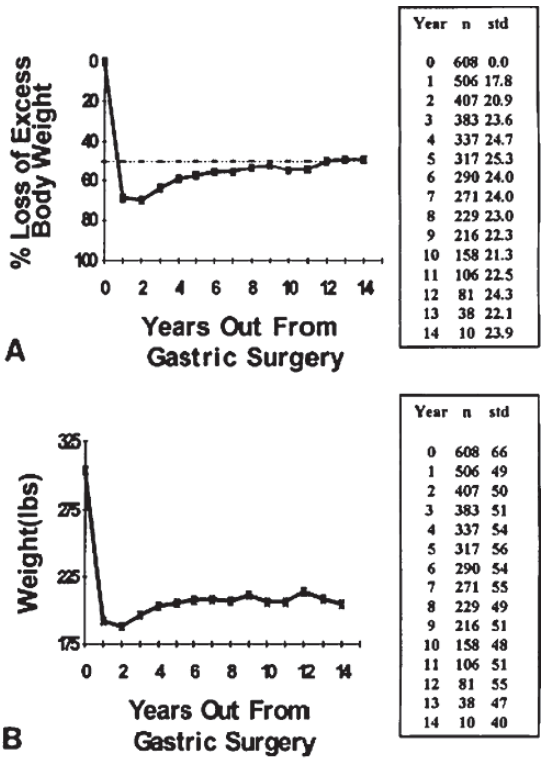



**Figure 3.** The gastric bypass produces durable weight loss. Weight loss of the entire cohort of 608 patients is shown in terms of pounds and percentage loss of excess body weight. If the patients with failed staple lines and stretched anastomoses are removed, the line is virtually straight.

**Fig. 7.** The gastric bypass produces durable weight loss. Weight loss of the entire cohort of 608 patients is shown in terms of pounds and percentage loss of excess body weight. If the patients with failed staple lines and stretched anastomoses are removed, the line is virtually straight (Graph from paries 14year follow-up).

2 diabetes as early as 1 mo postoperatively after BPD, when their excess weight was still more than 80% *(74)*. In addition, despite significant weight loss, many of these gastric bypass patients remain obese by definition. Hickey et al measured the levels of fasting plasma insulin, glucose, leptin, insulin sensitivity; and dietary habits in 6 morbidly obese women whose weight was stable after gastric bypass and 6 morbidly obese preoperative control subjects who also had a stable weight. Despite matching these patients for weight, body mass index, percent body fat, body fat distribution, metabolic rates, and age, the surgical patients had significantly lower serum leptin, fasting glucose, and fasting insulin, increased insulin sensitivity, and decreased food intake. This study suggests that the gastric bypass effect on type 2 diabetes is likely secondary to decreased caloric intake and/or change in gastrointestinal hormones rather than weight loss alone *(71)*.

Support of decreased caloric intake as a mechanism for the effect of obesity surgery on type 2 diabetes is shown in a study by Pories et al consisting of a sham operation. A patient who was taken to the operating room for a gastric bypass was unable to undergo completion secondary to a full stomach. Postoperatively, this patient received the same postoperative diet as those patients who had undergone the gastric bypass. The same normalization of plasma glucose and insulin levels was observed in this patient while he remained on the diet as in the patients who underwent gastric bypass. This experimental design is similar to pair-feeding experiments in animals and suggests that caloric restriction is sufficient to explain the improvement in type 2 diabetes after gastric bypass during active weight loss *(70)*.

The observation that restrictive-malabsorptive procedures result in superior control of glucose and insulin levels compared to the restrictive procedures suggests that the surgical bypass procedures may have a role, in addition to weight loss, in the resolution of type 2 diabetes. Therefore, restrictive-malabsorptive procedures should be given special consideration in patients with type 2 diabetes and type 3 obesity.

### *Clinical Considerations of Obesity Surgery*

It is particularly important that the surgical treatment of obesity be a team effort. Preoperative evaluation for sleep apnea and its postoperative management can be life saving. Dietary consultation and treatment to reduce hepatic fat can increase the ease and safety of the operative procedure. Stopping the use of exogeneous estrogens and instituting procedures to prevent thromboembolism are essential. Preoperative psychological evaluation to screen for depression, eating disorders, and other problems common to the severely obese, with postoperative follow-up, is of particular importance. The postoperative follow-up also involves management of pain without nonsteroidals, paying close attention to pulmonary hygiene and fluid balance, and insuring against vitamin and iron deficiency. Just as coronary bypass operations are done with greater safety in centers prepared to do them and practiced in the procedure, the same is true of obesity surgery, in general, and laparoscopic restrictive-malabsorptive procedures, in particular. In fact, Medicare has stopped reimbursement for obesity surgery except in designated Centers of Excellence, which have a team in place and a volume of surgery to insure optimal safety. For those interested in reading further on this subject, reference *(75)* is suggested.

## CONCLUSIONS

Treatment with obesity pharmaceuticals can result in a 5–10% weight loss that is clinically significant, but should be delivered in the context of a behavior and lifestyle change program, because such programs not only increase weight loss efficacy economically, but they also promote healthy living. Restrictive-malabsorptive obesity surgical procedures have beneficial effects on reversing type 2 diabetes above the weight loss they achieve, and should be the first consideration for a surgical procedure, if a surgical solution to the obesity is sought in a diabetic patient. In the case of medical therapy, physicians are often not prepared to administer the essential lifestyle modification program, which should accompany the use of pharmacological therapy. The surgical treatment of obesity is complex and requires interaction with dietitians and other health care professionals in addition to the surgeon. Thus, the optimal treatment of obesity is a team discipline, whether the treatment is surgical or medical. Fostering this interactive approach gives the best hope for optimal success in treating obesity and type 2 diabetes which have both been increasing steadily in prevalence since the early 1980s.

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# 21 The Liver in Type 2 Diabetes Mellitus

*Anna Mae Diehl and Steve S. Choi*

***CONTENTS***



**Summary**

Type 2 diabetes mellitus is associated with nonalcoholic fatty liver disease (NAFLD). NAFLD is a spectrum of hepatic pathology that ranges from simple steatosis, on the most clinically benign end of the spectrum, to cirrhosis on the opposite extreme where most liver-related morbidity and mortality occur. Nonalcoholic steatohepatitis (NASH) is an intermediate lesion characterized by noticeably increased rates of hepatocyte death, with accompanying inflammatory cell infiltration and variable degrees of fibrosis. Abdominal ultrasound surveys of adult diabetic populations suggest that at least half have hepatic steatosis. That fatty liver is common among patients with type 2 diabetes is not surprising because work with animal models indicates that fat accumulation within hepatocytes stimulates hepatic production of inflammatory cytokines that mediate muscle insulin resistance. Liver biopsy series of individuals with type 2 diabetes and hepatic steatosis demonstrate that liver damage has progressed to NASH in most and that a sizeable proportion have advanced fibrosis, with cirrhosis in some. There is growing evidence that liver disease contributes significantly to morbidity and mortality in patients with type 2 diabetes. Indeed, at least 3 recent studies indicate that liver-related mortality approaches death rates from cardiovascular disease and cancer in patients with type 2 diabetes and NASH. Because hepatic insulin resistance appears to play a pivotal role in the pathogenesis of NAFLD, treatment of NAFLD in individuals with type 2 diabetes focuses on optimizing insulin sensitivity with pharmacologic and life-style interventions. This approach appears to reduce steatosis, improve hepatic necroinflammation, and lessen fibrosis in many, but not all, patients. Individuals in whom liver damage progresses to cirrhosis are managed like patients who develop cirrhosis from other liver diseases. Treatment options for such individuals include orthotopic liver transplantation. Unfortunately, however, NAFLD often recurs in the engrafted organ, emphasizing the importance of life-long efforts to optimize insulin sensitivity in these patients.

**Key Words:** Nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; cirrhosis; hepatocellular carcinoma; metabolic syndrome; adipokines; inflammation; type 2 diabetes.

## ETIOLOGY OF LIVER DISEASE IN TYPE 2 DIABETES

Type 2 diabetes mellitus is associated with nonalcoholic fatty liver disease (NAFLD). NAFLD is a spectrum of hepatic pathology that ranges from simple steatosis (Fig. 1a and Color Plate 5, following p. 34), on the most clinically benign end of the spectrum, to cirrhosis (Fig. 1c) on the opposite extreme where most liver-related morbidity and mortality occur. Nonalcoholic steatohepatitis (NASH) is an intermediate lesion characterized by noticeably increased rates of hepatocyte death, with accompanying inflammatory cell infiltration and variable degrees of fibrosis (Fig. 1b). Hepatocyte injury and inflammatory cell infiltration generally are worse in the perivenous, than in the periportal, areas of the liver *(1)*. The pattern of fibrosis is typically pericellular and sinusoidal (dubbed "chicken wire fibrosis"), with fibrous septa bridging portal and perivenous areas as cirrhosis

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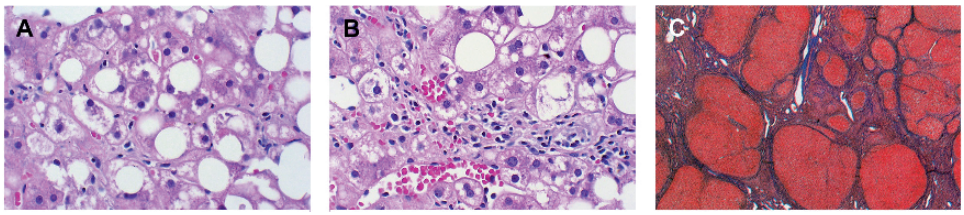


**Fig. 1.** Photomicrographs of macrovesicular steatosis (**A**), steatohepatitis with lymphocytic infiltrates (**B**), and macronodular cirrhosis (Fig. 1C) that demonstrate the range of NAFLD. (A and B courtesy of Dr. M. Gottfried, Department of Pathology, Duke University Medical Center) (*see* Color Plate 5, following p. 34).

evolves. Fibrosis is more common in NASH than in the more benign simple hepatic steatosis, the earliest stage of NAFLD, suggesting that NASH is a more advanced form of liver damage than NAFL.

## PREVALENCE OF NAFLD

Abdominal imaging studies, such as proton nuclear magnetic resonance (NMR) spectroscopy, permit accurate quantification of liver fat content and this noninvasive approach has been used to derive "normal" liver fat content, as well as to estimate the prevalence of hepatic steatosis in the general population. A recent proton-NMR study of over 2,000 adults in one urban area in the United States suggests that values for liver triglyceride content are $\leq$5.5% in healthy, nonobese individuals *(2)*. If values above this cut-off are considered to reflect abnormal hepatic accumulation of fat, about a third of the general population has hepatic steatosis. The prevalence of steatosis varies among different ethnic groups, being highest (45%) in Hispanic/Latino individuals, intermediate (33%) in whites and lowest (24%) in African Americans.

Surveys of adult diabetic populations with abdominal ultrasonography, which is relatively insensitive for detecting liver fat, show that at least half have hepatic steatosis, suggesting that fatty liver disease is much more common in patients with type 2 diabetes than in the general adult population *(3)*. This concept is supported by analysis of data from other population-based studies, such as the National Health and Nutrition Evaluation Survey (NHANES) III *(4,5)* and Dallas Heart Study *(2)*. Both suggest that type 2 diabetes is highly correlated with NAFLD.

Although advances in abdominal imaging technology have generated consensus that about one third of American adults have fatty livers, the proportion of these individuals that have more advanced forms of liver disease (i.e., NASH or cirrhosis or HCC) remains obscure. This uncertainty reflects the fact that current noninvasive tests do not reliably distinguish steatosis from steatohepatitis or stage the extent of liver fibrosis. Therefore, it has been impossible to define the proportion of NAFLD patients in the general population who have NASH or cirrhosis. As a result, most predictions about the overall burden of NASH and NAFLD-related cirrhosis have been extrapolated from findings in patients who undergo evaluations for suspected liver disease. An unavoidable drawback of this approach is that it might bias sampling in favor of more advanced liver damage. Mindful of this caveat, it is instructive to review recent reports about the relative frequencies of NASH and cirrhosis in different groups with NAFLD.

A recent review of health records from the predominantly Caucasian general population of Olmsted County, Minnesota, identified 420 individuals with a diagnosis of NAFLD. The prevalence of cirrhosis in this group was 5% and about 10% of the cirrhotic group developed hepatocellular carcinoma (HCC) *(6)*. A retrospective analysis of 247 Japanese patients with biopsy-proven NAFLD demonstrated a significantly higher prevalence of advanced fibrosis. In that study, cirrhosis was demonstrated in 17% and about a quarter of those with cirrhosis had co-incident HCC *(7)*. Advanced liver fibrosis (stage F3) was documented in an additional 18% of the Japanese patients, bringing the overall prevalence of stage F3-4 fibrosis to 35% in that population. Disparity in the prevalence of cirrhosis in these studies suggests that genetic or environmental factors might modify the prevalence of NAFLD-related cirrhosis. Of note, however, is the consistency of evidence that 10–20% of patients with NAFLD-related cirrhosis develop liver cancer.

Reports about liver histology obtained during bariatric surgery for morbid obesity also help us to determine the prevalence of NASH and cirrhosis in NAFLD. Moreover, because adults selected for bariatric surgery are relatively young and preoperative screening generally eliminates those with portal hypertension or significant liver blood test abnormalities, such studies are likely to provide a conservative estimate of the relative frequencies of NAFL, NASH, and NAFLD-related cirrhosis in a high-risk, morbidly obese population. A Chilean survey of 127 consecutive bariatric surgery patients demonstrated NAFL in 37%, NASH in 26%, and cirrhosis in 2% of their patients *(8)*. Recent analysis of liver histology from 689 US bariatric surgery patients demonstrated a similar prevalence of cirrhosis (i.e., 2%) *(9)*. Another study of a smaller group of bariatric surgery patients ($n$ = 39 patients) reported a somewhat higher prevalence of NAFL (49%) and NASH (44%), but an identical prevalence of cirrhosis (2%) *(10)*. Finally, when liver biopsies were performed in 212 consecutive bariatric surgery patients who had no cause for liver disease other than NAFLD, 93% were found to have NAFLD. Most of these had simple steatosis (i.e., NAFL), but 26% had NASH, and 9% had bridging fibrosis or cirrhosis *(11)*. Thus, in morbidly obese, relatively young adults with NAFLD who have been screened to eliminate those with clinical or laboratory evidence of advanced liver disease, the overall prevalence of NASH ranges from 26–44% and that of cirrhosis is about 2%.

As expected, the prevalence of advanced fibrosis in patients undergoing elective bariatric surgery is considerably lower than the 13.8% prevalence of severe fibrosis that was reported in an autopsy series of morbidly obese, nonalcoholic individuals *(12)*. However, the ~14% prevalence for advanced fibrosis in the autopsy series is fairly similar to the 17% prevalence of cirrhosis that was noted in much leaner Japanese NAFLD patients (see previous discussion). Both of these values resemble the 21% prevalence of advanced fibrosis that was noted in a recent biopsy series of 132 US patients with NAFLD *(13)*.

Hence, conservative interpretation of the aggregate data from population-based samples, bariatric surgery patients, and individuals who are referred for liver biopsy suggests that at least 2%, and as many as 17%, of NAFLD patients are cirrhotic. Others have bridging fibrosis, making the overall prevalence of advanced hepatic fibrosis in NAFLD higher than these estimates. For comparison, note that the prevalence of cirrhosis in NAFLD is within ranges that have been reported for nonhospitalized individuals undergoing evaluation for chronic hepatitis C (0.5–24) *(14,15)*. The prevalence of HCC in individuals with NAFLD is unknown. However, current evidence suggests that when HCC develops in NAFLD, it is virtually always in the context of cirrhosis. Recent, published series report HCC in as many as 10–20% of patients with NAFLD-related cirrhosis *(6,7)*.

Using the most conservative extremes of the aforementioned prevalence estimates to derive numbers of US adults afflicted with various stages of NAFLD generates the following approximations: 45 million US adults have NAFLD (30% of 150 million adults in the US), 11 million have NASH (25% of 45 million individuals with NAFLD), 900,000 have NAFLD-related cirrhosis (2% of 45 million with NAFLD), and 90,000 have HCC (10% of the 900,000 with NAFLD-related cirrhosis). For comparison, 3 million US adults have chronic hepatitis C (2% of 150 million US adults) and as many as 750,000 have hepatitis C virus (HCV)-induced cirrhosis (25% of 3 million with chronic HCV) *(14)*.

Liver biopsy series of individuals with type 2 diabetes and ultrasonographic findings of hepatic steatosis demonstrate that liver damage has progressed to NASH in most. In a recent study of patients from a diabetes clinic, 87% of those with fatty liver on ultrasound had NASH demonstrated by liver biopsy *(3)*. Similar results were noted in recent study in bariatric surgery patients. Also, in that group of morbidly obese subjects, having overt type 2 diabetes mellitus increased the risk for cirrhosis by 75-fold *(16)*. Hence, individuals with type 2 diabetes appear to differ dramatically from nondiabetics with NAFLD. Most type 2 diabetic patients with NAFLD have NASH with fairly extensive fibrosis, whereas most of the nondiabetics with NAFLD have simple steatosis *(17)*. Advanced fibrosis is an antecedent for cirrhosis in various types of chronic liver disease. Cirrhosis, in turn, generally increases the risk for HCC. The increased prevalence of NAFLD-related cirrhosis in type 2 diabetic populations may explain why type 2 diabetes is a risk factor for HCC *(18)*.

## PATHOGENESIS OF DIABETES-RELATED LIVER DISEASE

Over the last decade, considerable progress has been made in delineating the mechanisms that cause steatosis and steatohepatitis *(19)*. It remains less evident why only a minority of individuals with these "early" stages of fatty liver disease progress to cirrhosis or develop liver cancer.

Briefly, in the early stages of fatty liver disease, fat accumulates within hepatocytes when mechanisms that promote lipid removal (by oxidation or export) cannot keep pace with mechanisms that promote lipid import or biosynthesis. Although alcohol consumption has long been known to promote lipid biosynthesis while inhibiting lipid export, it has been appreciated only recently that the molecular mechanisms involved are very similar to those that promote steatosis in nonalcoholic fatty liver disease.

Three of the best-characterized factors that modulate the evolution of fatty liver disease are fatty acids, tumor necrosis factor α (TNFα), and adiponectin *(20–22)*. Fatty acids routinely traffic between the liver and adipose tissues. Fat and liver are also important sources of TNFα and adiponectin *(23)*. Interestingly, the latter 2 proteins regulate fatty acid turnover within hepatocytes. Adiponectin generally reduces lipid accumulation within hepatocytes by inhibiting fatty acid import and increasing fatty acid oxidation and export. It is also a potent insulin-sensitizing agent *(24)*. TNFα antagonizes the actions of adiponectin, and thereby promotes hepatocyte steatosis and insulin resistance.

Situations that increase TNFα relative to adiponectin promote hepatic steatosis and insulin resistance *(20)*. TNFα also increases mitochondrial generation of reactive oxygen species (ROS), promotes hepatocyte apoptosis, and recruits inflammatory cells to the liver. Hence, protracted exposure to TNFα generates oxidative and apoptotic stress that sometimes overwhelms antioxidant and antiapoptotic defenses, leading to steatohepatitis *(25)*. Studies in mouse models of NASH, as well as mice with ethanol-induced steatohepatitis, prove that overproduction of TNFα relative to adiponectin causes steatohepatitis, because treatments that inhibit TNFα or that increase adiponectin improve steatohepatitis in all of these models *(19)*. In addition, studies in humans with NASH demonstrate that the relative risk of developing steatohepatitis correlates with increases in TNFα or decreases in adiponectin levels *(26)*.

Given strong experimental and clinical evidence that unopposed TNFα activity promotes steatosis and steatohepatitis, it is interesting that there is now compelling evidence that the simple accumulation of fatty acids within hepatocytes is sufficient to trigger these cells to produce TNFα *(27)*. Fatty acids induce signaling in hepatocytes that activates kinases, such as Inhibitor Kappa Kinase (IKK) beta that, in turn, activate the Nuclear Factor-κB (NF-κB) transcription factor, driving hepatocyte synthesis of TNFα and IL-6 *(27,28)*. Recent studies in transgenic mice with hepatocyte-specific overexpression of IKK-beta demonstrate that hepatocyte-derived IL-6 is responsible for systemic insulin-resistance *(28)*. Therefore, like adipose tissue, fatty livers (and specifically, fatty hepatocytes) also make soluble factors that circulate to distant tissues and contribute to systemic insulin resistance (i.e., the metabolic syndrome).

Nonobese individuals can clearly develop alcohol-induced steatohepatitis *(29)*, and may also develop NASH *(30)*. The mechanisms for liver damage in nonobese and obese individuals may be similar, and involve excessive hepatocyte exposure to fatty acids, fatty acid-inducible inflammatory mediators (i.e., TNFα), and reactive oxygen species (ROS). In support of this concept, an important role for the intestinal microflora in regulating intestinal uptake of diet-derived lipids, as well as hepatic fatty acid synthesis, has been identified recently *(31)*. Thus, it is conceivable that the gut bacteria of some nonobese individuals might promote excessive hepatic accumulation of fatty acids, as well as exposure to other bacterial factors (e.g., lipopolysaccharide) that trigger hepatic TNF and ROS production. As in obese individuals, increased TNF would antagonize adiponectin activity, and promote steatosis, steatohepatitis, and insulin resistance.

It is generally believed that progression from fatty liver disease to cirrhosis is predominantly dictated by the severity of oxidant stress and consequent necroinflammation that occurs in individuals with steatohepatitis *(32,33)*. However, findings in animal models of steatohepatitis cast some doubt on this assumption because mice that develop severe steatohepatitis do not uniformly progress to cirrhosis *(34)*. In fact, progression to cirrhosis is also poorly predicted by the gravity of the injurious insult in human fatty liver disease. For example, although there is no doubt that alcohol is hepatotoxic, most lifelong heavy drinkers do not become cirrhotic *(35)*. Similarly, although obesity clearly increases exposure to fat-derived inflammatory mediators, some morbidly obese individuals have normal livers at the time of gastric bypass surgery *(36)*.

These apparent paradoxes might be explained by the fact that liver damage is determined by the adequacy of liver repair mechanisms, as well as the severity of a particular noxious insult. Individuals who are "poor repairers" suffer more net liver damage for any given level of injury than those who are "average repairers," whereas those who are "super repairers" may survive relatively unscathed, with little evidence of liver damage despite a significant

noxious exposure. Viewed from this perspective, individuals who merely develop steatosis despite constant bombardment with inflammatory factors might be "super-repairers," whereas those who develop steatohepatitis have only "average" repair capabilities, and the minority with "poor repair" abilities develop cirrhosis.

Indeed, the possibility that differences in repair responses might contribute to liver disease outcome merits consideration in fatty liver disease because this condition is often associated with obesity, and adipose tissue is an important source of various mediators that modulate wound-healing responses *(20–22)*. Indeed, hepatic stellate cells (HSC) express receptors for several of the adipose-derived factors that modulate HSC activation, including leptin, angiotensin, adiponectin, and norepinephrine *(37)*. Studies in mice demonstrate that leptin, angiotensin and norepinephrine promote HSC proliferation, upregulate HSC expression of profibrogenic cytokines, such as transforming growth factor-β (TGF-β), and induce collagen gene expression *(37,38)*. Conversely, adiponectin appears to inhibit HSC activation and decrease liver fibrosis *(39)*. It is likely that plasminogen activator inhibitor-1 (PAI-1) also regulates HSC because it has been shown to influence fibrosis in other tissues *(40)*.

Studies of patients with fatty liver disease support a role for adipose-derived factors in progression to cirrhosis. For example, obesity is an independent risk factor for cirrhosis in alcoholic fatty liver disease *(41)*. In addition, increases in adrenergic tone and angiotensin receptor activity mediate hypertension in individuals with the metabolic syndrome. Hypertension has been identified as an independent risk factor for advanced liver fibrosis in nonalcoholic fatty liver disease *(42)*. Consistent with the latter concept, a small open-label trial of angiotensin receptor blockade in individuals with NASH and hypertension suggested that this treatment decreased liver fibrosis and slowed disease progression *(43)*.

In summary, studies of animal models and patients with fatty liver disease suggest that the early-intermediate stages of this condition (i.e., steatosis and steatohepatitis) are caused by excessive exposure to fatty acids and inflammatory cytokines that induce hepatocyte steatosis, threaten hepatocyte viability, and promote hepatic and systemic insulin resistance. Resultant increases in the rate of liver cell death trigger repair responses. The latter are modulated by various factors that regulate the activation of hepatic stellate cells. In some individuals, the net effect of this process is "unhealthy" repair, with resultant cirrhosis. More research is needed to clarify the molecular basis for inter-individuals differences in repair responses that are triggered by chronic fatty liver injury. Improved understanding of such pathobiology should enhance identification of individuals who are at greatest risk for developing cirrhosis, as well as the development of effective treatments to abort disease progression.

## DIAGNOSIS OF NAFLD

### *History*

Like most patients with chronic liver disease, patients with NAFLD are typically asymptomatic or have nonspecific symptoms, such as fatigue and malaise *(44–46)*. Some complain of vague right upper quadrant pain, prompting a search for gallbladder, stomach or pancreatic disease. However, workup for such pathology is generally negative and cholecystectomy, sphincterotomy, or antireflux treatments seldom improve this symptom.

Suspicion of fatty liver disease is often engendered when liver enzyme elevations are noted incidentally, and hepatic steatosis is demonstrated during imaging tests. It is important to emphasize that there are 2 major types of fatty liver disease: alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD). Neither abdominal imaging tests nor liver histology can distinguish AFLD from NAFLD. Blood tests are also ineffective for this purpose. Hence, NAFLD can only be diagnosed after obtaining a careful history that excludes excessive alcohol consumption. To date, there have been no systematic studies to determine if type 2 diabetes lowers the threshold for alcohol-induced liver damage. "Safe" levels of alcohol ingestion are generally considered to be one or fewer drinks per day in women and 2 or fewer drinks per day in men (one drink = 10 g ethanol) *(47)*. Thus, fatty liver is presumed to be owing to NAFLD in individuals who drink less than this, and who lack other reasons for hepatic steatosis, such as certain heritable conditions or ingestion of steatosis-inducing drugs (Table 1).

### *Physical Examination*

Physical examination of patients with NAFLD is generally most notable for overweight/obesity and mild-modest hepatomegaly *(44–46)*. Some patients exhibit overt features of insulin resistance, such as acanthosis nigricans or multiple skin tags. Signs of parenchymal failure, such as jaundice or coagulopathy, and portal hypertension, such

Table 1
Levels of evidence for therapeutic interventions for NAFLD

| *Therapeutic approach* | *Grade of recommendation* | *Clarity of risk/benefit* |
|---|---|---|
| Measures to Reduce Adiposity | | |
| Diet and exercise | 1B | Clear |
| Intestinal fat absorption inhibitors | 1C+ | Clear |
| Bariatric surgery | 1C | Clear |
| Inhibitors of Inflammation and Oxidant Stress | | |
| Vitamin E | 2B | Unclear |
| Betaine | 2B | Unclear |
| S-adenosylmethionine | 2C | Unclear |
| Silymarin | 2C | Unclear |
| Pentoxifylline | 2C | Unclear |
| Probiotics | 2C | Unclear |
| Thiazolidinediones | 2B | Unclear |
| Insulin-sensitizing agents | | |
| Metformin | 2B | Unclear |

as spider angiomata, palmar erythema, splenomegaly, ascites, lower extremity edema, and/or encephalopathy are unusual, and signify that the liver disease has progressed to cirrhosis.

## *Blood Tests*

Although elevated levels of serum aspartate and/or alanine aminotransferases (AST, ALT) and alkaline phosphatase (AP) are typically used to identify individuals who may have liver disease, these tests can be entirely normal in individuals with NAFLD *(48)*. Moreover, liver enzyme values in NAFLD are seldom increased more than 5-fold, and the magnitude of the abnormalities in these tests correlates poorly with the degree of tissue damage found on liver biopsy *(45,46)*. As in other liver diseases, serum albumin and bilirubin, prothrombin time and platelet count are better indicators of hepatic reserve, with decreases in albumin and/or platelet count and increases in bilirubin and/or prothrombin time heralding advanced liver damage. The latter is also suggested by progressive decline in AST values, particularly when the ratio of ALT to AST values exceeds 2 *(46)*. A high ALT to AST ratio also raises concern that AFLD, rather than NAFLD, is causing the liver damage *(49)*.

Much current research is focused on developing novel biomarkers that can distinguish early from advanced liver damage in various liver diseases, including NAFLD. To date, no one test or panel of markers is sufficient to accomplish this task because test values in individuals with different degrees of liver damage tend to overlap *(50)*. As a result, only a few of these putative fibrosis markers have become clinically available *(51)*. Values for such tests tend to be much lower in subjects who have little or no liver damage than in those with more significant liver injury. Hence, very low or normal fibrosis marker results tend to have a reasonably good negative predictive value and may be useful in identifying a subset of NAFLD patients who are unlikely to have advanced fibrosis *(52)*.

Unlike many other types of chronic liver disease, NAFLD cannot be identified by any one blood test. Thus, it remains a diagnosis of exclusion that is suggested when blood tests for other causes of chronic liver disease, such as viral hepatitis, iron overload, copper accumulation, α-1 antitrypsin deficiency and autoimmune liver diseases, are negative. However, emerging evidence demonstrates that NAFLD may coexist with other liver diseases, such as hepatitis C or iron overload, and worsen their prognosis *(46,53)*. In addition, it has become apparent that antinuclear antibody and other autoantibodies are often increased in patients with NAFLD, confounding efforts to distinguish NAFLD from autoimmune hepatitis without liver histology *(54)*.

In individuals with elevated aminotransferases or steatosis on abdominal imaging studies (see below) and negative tests for other liver diseases, evidence for other parameters of the metabolic syndrome provide additional support for the diagnosis of NAFLD *(55)*. Patients with type 2 diabetes already have a major component of the

metabolic syndrome, namely insulin resistance, and findings of dyslipidemia (increased total cholesterol, low high density lipoprotein values, hypertriglyceridemia), and/or hyperuricemia further strengthen the likelihood that NAFLD is their underlying liver disease.

### *Imaging Studies*

The accumulation of fat within hepatocytes is the hallmark of NAFLD. This can be demonstrated by various abdominal imaging tests, including ultrasound, CT scan, or magnetic resonance imaging. Currently, the most sensitive approach to detect fatty liver is proton-nuclear magnetic resonance (NMR) spectroscopy, a technique that permits accurate quantification of hepatic fat content *(2)*.

Although proton-NMR spectroscopy is the most sensitive, noninvasive technique for estimating liver fat content, this approach is not widely used in practice because of its expense and relatively limited availability. Instead, abdominal ultrasonography is the most popular approach for evaluating hepatic fat *(46)*. Although the ease and relatively low cost of abdominal ultrasound justify this practice, sonography is far less sensitive than proton-NMR spectroscopy for detecting hepatic steatosis, and probably misses many cases. In addition, the echo pattern that suggests hepatic steatosis is nonspecific, and misclassification of other types of liver damage as fatty liver can occur. Mindful of these caveats, ultrasonography is reasonably useful for identifying hepatic steatosis. However, all noninvasive imaging tests are relatively insensitive for estimating the severity of liver damage and fibrosis because portal blood flow must be altered sufficiently to induce splenomegaly, varices and/or ascites before a diagnosis of cirrhosis is even suggested by abdominal imaging studies.

### *Liver Biopsy*

The lack of specific blood tests for NAFLD, and the limited capability of abdominal imaging tests to detect liver damage and fibrosis, make liver biopsy the most reliable test for diagnosing and staging NAFLD *(46)*. Although invasive, liver biopsy is a relatively safe procedure that is generally done in an outpatient setting without sedation. Biopsy-induced bleeding is the major cause of significant adverse events *(56)*. Clinically significant bleeding occurs in fewer than 1 in 1,000 procedures, provided patients are screened to eliminate individuals who are taking medications that interfere with platelet or clotting factor function or who have prothrombin times above 15 s and/or platelet counts below 75,000/mL. Patients with coagulopathy can undergo liver biopsy via a transvenous or laprascopic approach, but still have a somewhat increased risk for bleeding from the biopsy site.

The main justification for liver biopsy is that the acquired tissue permits reliable estimation of the cause and stage of liver damage *(57)*. Indeed, liver histology is very useful in distinguishing fatty liver disease from other causes of chronic hepatitis. On the other hand, as mentioned earlier, biopsy cannot differentiate AFLD from NAFLD as the cause of steatosis or steatohepatitis. Also, when liver damage has progressed to cirrhosis, steatosis and steatohepatitis sometimes disappear, making it difficult to prove that NALFD was the cause for cirrhosis. Such cases are generally given a histologic diagnosis of cryptogenic cirrhosis. Retrospective reviews of cryptogenic cirrhosis cases from several centers suggest that up to 70% occur in individuals who have risk factors for NAFLD (particularly type 2 diabetes and/or obesity), some of whom had an earlier liver biopsy that demonstrated steatosis or steatohepatitis *(58–60)*. Thus, liver biopsy is generally an effective strategy for confirming the clinical suspicion of NAFLD by excluding other causes of chronic hepatitis. The latter is most helpful in patients with type 2 diabetes who have serologic evidence for iron overload, autoimmune disease, or infection with hepatitis viruses.

Biopsy is also the current gold standard for staging the extent of liver damage and fibrosis in all types of chronic liver disease, including NAFLD. Unfortunately, however, sampling error somewhat limits test performance in this regard *(61)*. Tissue cores that are smaller than 1.5 cm in length, particularly those that are obtained with small-diameter biopsy needles, may provide false estimates of overall liver damage and fibrosis *(62)*. Even seemingly adequate samples are subject to sampling artifact, as demonstrated by a recent study that showed variations in the damage grade and fibrosis stage when liver cores were obtained by inserting the biopsy needle at different angles *(63)*. Nevertheless, despite these limitations, biopsy is currently the most sensitive and specific means for judging the severity of liver damage and fibrosis.

Recently, an NIH-supported consortium of hepatic pathologists, generated standards for grading and staging NAFLD *(64)*. These criteria have been dubbed the NASH Clinical Research Network (CRN) scoring system or NAS. Biopsy samples are rated for steatosis, hepatocyte injury (demonstrated by ballooning, Mallory hyaline

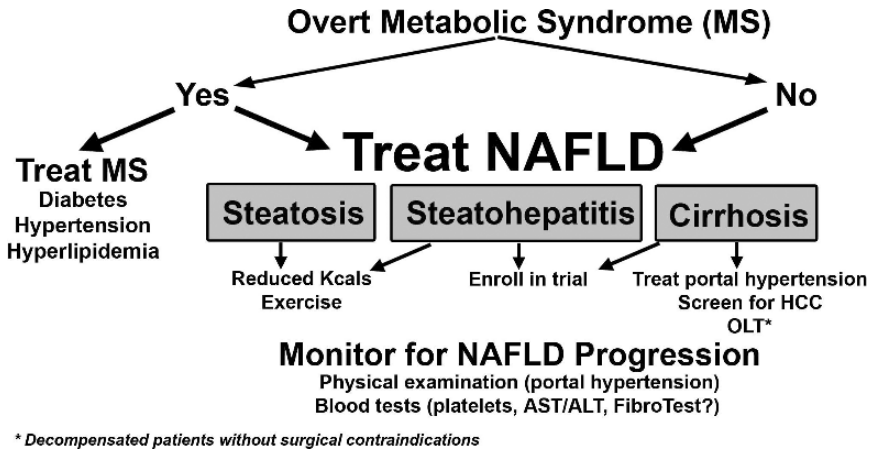


**Fig. 2.** This figure summarizes a diagnostic algorithm that can be used to evaluate individuals who are at high risk for NAFLD. The latter include people with the metabolic syndrome, those who have already had fatty liver demonstrated by some type of abdominal imaging test, and individuals who have elevated values of serum aminotransferases (AST, ALT) or unexplained (cryptogenic) cirrhosis.

inclusions, apoptosis), infiltration with inflammatory cells, and extent and distribution of fibrosis. As in other scoring systems, fibrosis is deemed to be advanced when fibrous septae bridge portal and/or central areas of liver lobules. A diagnosis of cirrhosis requires demonstration of nodules of hepatic parenchyma surrounded by fibrotic bands.

### *Algorithm for NAFLD Diagnosis*

Based on the earlier discussion, it is evident that combinations of diagnostic modalities, including history, physical examination, blood testing, imaging studies, and liver biopsy are generally used to establish the diagnosis of NAFLD. A useful approach is summarized in the accompanying algorithm (Fig. 2).

## NATURAL HISTORY AND PROGNOSIS OF NAFLD ASSOCIATED WITH TYPE 2 DIABETES

As discussed earlier, general knowledge about the natural history of NAFLD has been limited by the lack of sensitive, noninvasive diagnostic tests, and the dearth of population-based studies that include subjects who have undergone sequential liver biopsies. Nevertheless, sufficient data have accumulated that permit crude estimate of the prevalence of NAFL, NASH, and NALFD-related cirrhosis in the general adult US population. In addition, follow-up studies of selected subpopulations of NAFLD patients are increasing understanding about the risk for progressive liver damage and liver-related morality in this condition.

Two studies, one from a tertiary referral center in the U.S. and another from a Liver Center in Europe, suggest that age greater than 45–50 yr is the single best predictor of which adult patients referred for evaluation of unexplained aminotransferase elevations have bridging fibrosis *(65,66)*. The fact that older age is associated with liver fibrosis in NAFLD is reminiscent of findings in chronic hepatitis C, in which older age at infection increases the risk for liver fibrosis *(67)*. However, other factors clearly impact on the risk for liver fibrosis in NAFLD because there are many reports of young individuals with NAFLD-related fibrosis.

In general, young individuals with NAFLD-related hepatic fibrosis have comorbid conditions that are associated with severe insulin resistance, such as hypothalamic tumors or polycystic ovary syndrome, in addition to obesity *(68,69)*. Insulin resistance also identifies the subgroup of older, obese adults who are most likely to have liver fibrosis. Both the US and French studies cited earlier found that type 2 diabetes and overweight/obesity independently attributed risk for advanced hepatic fibrosis in NAFLD *(65)*. This concept is supported by data from a recent study in bariatric surgery patients. In that group of morbidly obese subjects, having overt type 2 diabetes mellitus increased the risk for cirrhosis by 75-fold *(16)*. Obesity has also been identified as a risk factor for fibrosis in alcohol-induced liver damage, chronic hepatitis C, and hemochromatosis *(70,71)*. Whether

or not obesity increases the general risk for liver fibrosis simply by increasing the risk for insulin resistance is unknown.

Although the concept that advanced liver disease is relatively common among adults with type 2 diabetes is not widely appreciated, a growing body of literature supports the concept that liver disease contributes significantly to mortality in this population. Overall, liver disease is the third leading cause of death in individuals who carry a diagnosis of NAFLD, compared to the thirteenth cause of death in the general adult population *(6)*. Liver disease outcomes may be even more lethal in NAFLD patients with type 2 diabetes. One recent study of patients with type 2 diabetes and NAFLD found that liver-related mortality outstripped death from cardiovascular disease and cancer, which are typically the top 2 killers in diabetic populations *(72)*. Hence, a significant (and growing) body of published data demonstrates that liver disease is both common and clinically significant in individuals with type 2 diabetes.

## MANAGEMENT OF DIABETES-ASSOCIATED LIVER DISEASE

Given the caveat that relatively few long-term follow-up studies of patients with NAFLD have been reported, the accumulating data about liver-specific outcomes are very consistent *(6,7,73–75)*. First, it is apparent that in NAFLD, as in other liver diseases, liver-specific morbidity and mortality are largely restricted to individuals who develop cirrhosis. Second, as in other liver diseases, in NAFLD, cirrhosis may be clinically inconspicuous for years before overt complications of portal hypertension or liver cancer emerge. Third, patients with advanced fibrosis owing to NAFLD are at risk for hepatocellular cancer (5-yr cumulative incidence as high as 20%) and death from liver disease (10-yr liver-related mortality rates as high as 11%). Fourth, like many other causes of chronic hepatitis, NAFLD often recurs after liver transplantation *(76)*.

The natural history of NAFLD validates interventions to arrest and/or reverse progressive liver damage. Current treatment approaches are guided by knowledge of NAFLD pathogenesis. As discussed earlier, the latter is thought to be driven by chronic exposure to excessive inflammatory mediators. These inflammatory factors are often produced by adipose tissue, but can also arise from other sources, including hepatocytes themselves, as well as other types of cells that reside in the liver. Chronic inflammation, in turn, induces chronic oxidative stress and insulin resistance. These conditions eventually overwhelm cellular defense mechanisms, resulting in liver damage. In some individuals, liver repair mechanisms cannot keep pace with this damage and fibrous tissue accumulates, eventually resulting in cirrhosis. Persistent efforts to remodel damaged livers also provide a tissue environment that promotes neoplasia, explaining why liver cancers sometimes develop in the setting of advanced NAFLD.

### *Specific Therapies for NAFLD*

The following therapeutic interventions are reasonable based on our current understanding of NAFLD pathogenesis *(77)*: measures to reduce adiposity (e.g., diet and exercise, intestinal fat absorption inhibitors, and bariatric surgery), inhibitors of inflammation and oxidant stress (e.g., vitamin E, betaine, S-adenosylmethionine, silymarin, pentoxifylline, and probiotics), insulin sensitizing agents (TZDs, metformin—these agents also inhibit inflammation), and antifibrotics (PPAR-gamma agonists, including TZDs) (Table 1). A cursory review of this list demonstrates that certain putative treatments, such as TZDs, inhibit multiple steps in disease pathogenesis, making these particularly attractive therapeutic candidates. However, these drugs may also cause potentially adverse consequences, including weight gain, in some individuals. Thus, before recommending these (or other) agents as generalized treatments for NAFLD, larger, prospective controlled trials are needed to confirm their safety and efficacy in these patients. At present, treatment recommendations for patients with NAFLD are guided by the severity of their liver damage.

In many patients with type 2 diabetes and NAFLD, treatment with insulin secretagogues or insulin itself is necessary to achieve glucose control. Such approaches may lead to intermittent hyperinsulinemia. Although excessive exposure to insulin appears to play a role in the pathogenesis of hepatic steatosis in some settings *(78)*, it is not known if treatments that increase circulating insulin levels have any impact on NAFLD progression in type 2 diabetic patients. Therefore, at this point, no recommendations can be made about adjusting particular diabetes medications in diabetic patients with NAFLD.

## *General Management of Patients with Chronic Liver Disease*

### Monitor Disease Progression

Regardless of which approach is selected specifically to treat NAFLD, all patients with NAFLD merit routine follow-up to monitor for evidence of progressive liver disease *(79)*. The latter generally includes bi-annual physician visits and blood work. Markers of liver injury (e.g., liver enzymes), as well as indicators of hepatic reserves (e.g., bilirubin, albumin, prothrombin time), and portal hypertension (platelet count) are monitored. Because existing tests are relatively insensitive for detecting progression of hepatic fibrosis, whether or not periodic liver biopsies are warranted has been debated in various types of chronic liver disease, including NAFLD. At this point, there is no consensus as to the optimal approach. However, liver biopsy to stage fibrosis may be justified in individuals with a high risk for progressive liver damage, such as those with NASH on index biopsy or who develop physical or laboratory findings suggestive of emerging portal hypertension during follow-up.

### Treat/Prevent Conditions that could Exacerbate Liver Damage

General surveillance for other aspects of the metabolic syndrome is also performed by routinely assessing lipid profiles, glucose control, and degree of hypertension. Treatments are adjusted to optimize management of dyslipidemia and diabetes. Most hepatologists also vaccinate patients with NAFLD to protect them from superimposition of hepatitis A and B.

### Prevent/Palliate Complications of Portal Hypertension

Individuals with cirrhosis require careful scrutiny for potential sequelae of portal hypertension, including varices, ascites, encephalopathy, and liver cancer *(80)*. Once cirrhosis is diagnosed, upper endoscopy is performed to screen for esophagogastric varices. Patients with large esophageal varices are candidates for beta-blocker prophylaxis to prevent variceal rupture. If beta-blockers are not tolerated owing to unacceptable hypotension, fatigue or exacerbation of hepatic encephalopathy, prophylactic banding of large esophageal varices merits consideration. Those without large varices on the initial exam undergo repeat endoscopy every 3–5 yr to monitor for emerging varices. Individuals with ascites are treated with salt-restricted diets and may also require diuretics, therapeutic paracentesis, or transvenous intrahepatic portal systemic shunting (TIPS). Those who exhibit symptoms or signs of encephalopathy are treated with lactulose. Patients with cirrhosis owing to NAFLD are also candidates for bi-annual abdominal imaging to screen for liver cancer. Screening recommendations for HCC in patients with NAFLD-related cirrhosis are similar to those with cirrhosis owing to other liver diseases *(81)*. MRI is probably the most sensitive approach, followed by contrast-enhanced, dynamic CT scan, with ultrasonography being the least sensitive modality. However, once a liver mass has been excluded by initial screening with MRI or CT, most practitioners rely on follow-up ultrasound examinations coupled with testing for serum alpha-fetoprotein to monitor for HCC. Rising levels of AFP and/or detection of a new liver mass in a cirrhotic patient generally implies that HCC has developed and triggers referral for definitive diagnosis and management.

### Refer Appropriate Candidates for Liver Transplanation

Similar to patients with decompensated cirrhosis from other types of chronic liver disease, NAFLD patients with decompensated cirrhosis or who develop small hepatocellular carcinomas localized to the liver should be referred to transplant centers for consideration of orthotopic liver transplantation *(82)*. Unfortunately, vascular complications of type 2 diabetes increase the mortality of liver transplantation, making this approach an untenable option for many patients with type 2 diabetes and NAFLD-induced cirrhosis or HCC. Immunosuppressive medications that are routinely used following liver transplantation also exacerbate insulin resistance and complicate diabetes management following liver transplantation. In addition, NAFLD often recurs in the engrafted liver, and cases of rapidly progressive cirrhosis have been reported *(76,83,84)*. Despite these limitations, recent data from the Unified Network for Organ Sharing (UNOS) demonstrate that cryptogenic cirrhosis (most of which is caused by advanced NAFLD) is one of the leading indications for liver transplantation in US adults *(85,86)*.

## FUTURE DIRECTIONS

A better understanding of the mechanisms that regulate repair of chronically injured livers is necessary to devise better noninvasive tests for advanced NAFLD. Because liver damage results from unsuccessful efforts to repair ongoing liver injury, there have been efforts to predict liver fibrosis by quantifying levels of injury-inducing factors, such as lipid peroxidation. This approach is based on the assumption that worse fibrosis is likely the result of greater levels of liver injury. In support of this concept, a recent study reported a correlation between serum thiobarbituric acid levels (TBARS) and liver fibrosis in patients with NAFLD *(10)*. Unfortunately, others have not been able to reproduce this success *(87)*.

Because recovery from liver injury requires repair, another strategy might be to look for early difference in repair responses to identify those who are likely to accumulate liver fibrosis as a result of NAFLD. This approach appears to have some merit because it has been shown that the number of activated, alpha smooth muscle actin-positive stellate cells on index liver biopsy is higher in individuals whose subsequent biopsy demonstrates advanced fibrosis than in those who do not become fibrotic *(88)*. Genetic testing for polymorphisms in genes that regulate liver damage is an extension of these strategies, but it offers several advantages. First, because testing is done on DNA from peripheral blood, the necessity for liver biopsy is obviated. Second, genetic polymorphisms "fingerprint" individuals, and do not change over time. Thus, testing for risk of disease progression can be done as soon as the disease is diagnosed, maximizing the time for preventative interventions. The use of genetic testing to predict the severity of liver damage is suggested by findings of a recent Australian study.

In that study, a large number ($n = 326$) of patients with hepatitis C infection of known durations underwent diagnostic liver biopsy. Patients were then categorized as either "slow" or "rapid" fibrosers based on their histologic stage of fibrosis and duration of HCV infection *(89)*. Slow fibrosers had none or very localized fibrosis (F0-F1) after 20 or more years of infection. Rapid fibrosers had either extensive, bridging fibrosis (F3) or cirrhosis (F4), or moderate bridging fibrosis (F2) after 10 or fewer years of infection. Both groups were then genotyped to identify polymorphisms in genes that have been linked to liver fibrosis (hereditary hemochromatosis, HFE; microsomal triglyceride transfer protein, MTP; apoplipoprotein E, APOE; chemokine receptor 5, CCR5; superoxide dismutase 2, SOD2; cytotoxic T lymphocyte antigen 4, CTLA4; low density lipoprotein receptor, LDLR; and myeloperoxidase, MPO). The findings support the investigators' hypothesis that rapid fibrosers inherit more fibrosis-associated polymorphisms than slow fibrosers. The adjusted odds ratios for the fibrosis-associated polymorphisms in 6 of the 8 genes (HFE, MTP, APOE, CCR5, SOD2) were 2.8–4.5-fold higher in rapid fibrosers. In addition, the odds ratio for rapid fibrosis increased with gene dose. None of the slow fibrosers inherited more than 2 fibrosis-associated polymorphisms, whereas most of the rapid fibrosers had inherited 5. Moreover, the adjusted odds ratio for rapid fibrosis increased with the number of fibrosis-associated polymorphisms, being 9-fold higher in patients with 3 polymorphisms, 15-fold higher in those with 4 polymorphisms and 24-fold higher in individuals with 5 or more polymorphisms than those with 2 or fewer polymorphisms. These results are very exciting because they suggest that the outcome of liver injury is largely predetermined by genetic factors. If confirmed by future studies, this finding implies that long-term monitoring and treatment efforts might best be focused on individuals with NAFLD (and other liver diseases) who are genetically predisposed to liver fibrosis. However, despite these encouraging results, it is premature to use genetic testing to define risk for liver disease progression until these findings are validated in more ethnically diverse populations with NAFLD.

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# 22 Developing Criteria for Defining Type 2 Diabetes in Pregnancy

*Lois Jovanovic and Seanna Martin*

***CONTENTS***



**Summary**

In 1997, the American Diabetes Association (ADA) announced new diagnostic criteria *(1)* for diabetes and set the definition of gestational diabetes (GDM). Before 1991, GDM was defined as "a transient abnormality of glucose tolerance during pregnancy" *(2,3)*. However, the 1997 definition of GDM by the ADA includes diabetes mellitus diagnosed during pregnancy. This definition ignores the added risks to the mother and to the fetus when the mother has undiagnosed type 2 diabetes. The epidemic of obesity and the increased prevalence of type 2 diabetes necessitate a reconsideration of the definition that would separate diabetes and slightly abnormal carbohydrate metabolism, so called "GDM" to provide a better model of care for type 2 diabetic pregnant women.

This chapter discusses the current literature that underscores the need for a unique diagnosis for those women with moderate to severe hyperglycemia and/or other evidence of long-standing diabetes complications. The label of gestational diabetes mellitus (GDM) is not adequate to identify the urgent need for more intensive surveillance and treatment with the use of multiple insulin injections in those women for type 2 diabetes in pregnancy.

**Key Words:** Gestational diabetes; pregestational type 2 diabetes; diabetes and pregnancy; screening and diagnosis of diabetes in pregnancy.

## DEFINITION OF GESTATIONAL DIABETES

O'Sullivan defined GDM as" "a transient abnormality of glucose tolerance during pregnancy" *(2)*. By the Third International Gestational Diabetes Workshop, the definition of gestational diabetes had been broadened to include "glucose intolerance of variable severity with onset or first recognition during pregnancy" *(4)*. When this definition is applied to all women who are first diagnosed with diabetes during pregnancy, the woman with type 2 diabetes falls under the same classification as a woman with true gestational diabetes, a much lower risk condition.

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## EVIDENCE THAT TYPE 2 DIABETES COMPLICATES PREGNANCY AND CAN BE DIFFERENTIATED FROM GDM DESPITE PRESENTING DURING PREGNANCY

Type 2 diabetes may well be more common than gestational diabetes when properly diagnosed *(5)*. In a report by Omori and Jovanovic *(6)*, 1,416 pregnant Japanese women who had risk factors for GDM were given a glucose tolerance test (OGTT) and evaluated based on the Japanese criteria for GDM of 2 or more values above: fasting >100 mg/dL, 1 h >180 mg/dL, 2 h >150 mg/dL. The frequency of GDM in first trimester is highest (33/250 [13.2%]), followed by the second trimester (32/417 [7.7%]), and third trimester (37/749 [4.9%]). Using the Japanese Diabetes Association's definition of type 2 diabetes in pregnancy as fasting glucose greater than 140 mg/dL, with evidence of retinopathy or a fetal malformation, the frequency of type 2 diabetes was 6.0% in the first trimester, 2.6%, in the second trimester, and 1.3%, and in third trimester. Thus, in this Japanese cohort of women with a positive glucose tolerance test, GDM accounted for 7.2%, and type 2 diabetes, diagnosed by the authors' criteria, accounted for 2.5% of the total pregnant population. In other words, 35% of women with a positive OGTT had type 2 diabetes diagnosed for the first time in pregnancy.

In this cohort the congenital malformation rate from GDM patients was 1.9%, no different from the rate in the general Japanese population. In contrast, the congenital malformation rate in infants of type 2 diabetic mothers diagnosed during pregnancy was higher than that of children from pregestational diabetic mothers treated during pregnancy: 12.7% versus 4%, respectively *(6)*.

There were no GDM patients with retinopathy. However, the rate of background retinopathy was 12.7% and proliferative retinopathy was 4.2% in the type 2 diabetic women diagnosed for the first time during pregnancy.

This report underscores the need for a separate classification to be made for type 2 diabetes that complicates pregnancy. All of these women would have only been called gestational diabetic women in the United States and may not have received the needed care for their comorbidities.

Similar rates and complications were seen in a cohort of pregnant Mexican American women in Santa Barbara, California where a total of 49,861 pregnancies occurred from 1997–2004 *(6)*. A total of 4,133 (8.3%) had a positive OGTT based on the ADA criteria (fasting greater than 95 mg/dL, 1 h greater than 180 mg/dL, 2 h greater than 155 mg/dL and a 3 h greater than 140 mg/dL) *(1)*. However, 40% of the "GDM" women, had type 2 diabetes first diagnosed during pregnancy based on our criteria: presence of acanthosis nigricans or insulin requirement before the twelfth wk of gestation owing to failure to maintain glucose goals with dietary intervention alone (data not published. Five percent of the type 2 diabetic women had retinopathy, and 7% had significant proteinuria at time of diagnosis *(9)*.

## EVIDENCE THAT TYPE 2 DIABETES IN PREGNANCY IS ASSOCIATED WITH INCREASED MATERNAL AND FETAL COMPLICATIONS

The ADA definition, although currently accepted in medical practice, has one apparent flaw. Type 2 diabetes in pregnancy needs to be differentiated from gestational diabetes because it is a more severe disease associated with longstanding glucose intolerance. GDM patients are very different because they develop impaired glucose tolerance only during the second half of pregnancy, and regain normal tolerance following the birth of their child.

There are several problems associated with confusing type 2 diabetes with GDM. First, in a woman with type 2 diabetes, the entire pregnancy is associated with glucose intolerance, not just the second half, as in GDM. Second, the rate of congenital malformations in the newborns is higher in women with type 2 diabetes. Finally, undiagnosed diabetic retinopathy is common in type 2 patients but not in patients with gestational diabetes *(6,7)*. As for the maternal dangers of hyperglycemia during pregnancy, patients with type 2 diabetes have more serious complications such as nephropathy and retinopathy *(11)*.

Because high blood glucose concentrations are present in the entirety of gestation for a mother with type 2 diabetes, this hyperglycemia interferes with organogenesis that takes place in the first 7 wks of pregnancy. Maternal hyperglycemia during this time contributes to increased rates of fetal malformation *(10,11)* and spontaneous abortions *(12)*. Hyperglycemia can also lead to macrosomia, birth injury, respiratory distress syndrome, and metabolic abnormalities *(4)*. Additionally, children of hyperglycemic mothers are more likely to develop type 2 diabetes later in life *(12)*.

## EVIDENCE THAT TYPE 2 DIABETES IN PREGNANCY IS ASSOCIATED WITH THE COMPONENTS OF THE METABOLIC SYNDROME

Other studies have demonstrated that patients with "GDM" are often actually a mix of type 2 diabetes patients and those with true gestational diabetes; however, there is no way to differentiate between them. For example, Sinha et al noted a high frequency of postpartum glucose intolerance in Asian women with what they termed "early onset GDM" (before 20 wk), and attributed this to undiagnosed type 2 diabetes in pregnancy *(14)*. Even the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus is aware of this difference *(1)*, but only suggests reclassifying the woman at least 6 wks after pregnancy ends to determine if she has regained glucose tolerance.

Some authors have postulated that features of the metabolic syndrome and insulin resistance might be used to identify women with type 2 diabetes in pregnancy. In a cohort of Mexican American pregnant women in Santa Barbara, California a total of 49,861 pregnancies occurred between 1997 and 2004. A total of 4,133 (8.3%) had a positive OGTT based on the ADA criteria *(6)*. Those women who had the highest glucose values on the glucose tolerance test and who were unable to maintain normoglycemia with diet alone had the highest glycosylated hemoglobin (A1C) values at the time of the glucose tolerance test (data not published). In addition they were also the heaviest and had the highest BMI. A high A1C value early in pregnancy indicates previous diabetes, whereas impaired glucose tolerance owing to the pregnancy itself (i.e., GDM) has its onset in later gestational weeks and is not associated with increase A1C. A high body mass index (BMI) is also a condition associated with type 2 diabetes, and is another valuable factor in diagnosing the type of diabetes a pregnant woman has. Elevated blood pressure may also be a marker of type 2 diabetes in pregnancy; the women in the cohort studied also had the highest blood pressures.

Lastly, glucose challenge test (GCT) and oral glucose tolerance test (OGTT) results may be used to help differentiate between gestational diabetes and preexisting type 2 diabetes. A GCT consists of 50 g of oral glucose drink given in the random state and a positive test is defined as a 1 h after the drink of greater than 140 mg/dL. Those women who have a positive GCT and then given the diagnostic test called the oral glucose toelrance test or OGTT consisting of 100 grams of glucose and blood glucose levels tested at 3 times: fasting, 1 h, 2 h, and 3 h after the drink. A positive OGTT is defined as 2 or more values above the cutoffs of fasting >95 mg/dL, 1 h >180 mg/dL, 2 h greater than 155 mg/dL and a 3 h > 140 mg/dL. The women who have a fasting greater than 95 mg/dL and/or glucose values greater than 200 mg/dL require insulin therapy. Values this high are strongly suggestive of type 2 diabetes not just new onset gestational diabetes *(1)*.

In a retrospective cohort analysis of Mexican American women, ages 15–45 yr, ($n = 92$) attending the Santa Barbara County Public Health Department pregnancy clinic (data not published), the predictive value for type 2 diabetes of A1C, BMI, blood pressure, glucose challenge (GCT) and OGTT results, and the extent or presence of acanthosis nigricans was assessed. All of the women were diagnosed with diabetes based on the glucose challenge and glucose toelrance tests, with the overwhelming majority classified as having gestational diabetes mellitus. Forty percent had evidence of acanthosis nigricans, a possible marker for long-standing insulin resistance. A complete data set (which included A1C values, BMI and blood pressure) was available for 51 women.

The highest recorded A1C value during pregnancy was used in the analysis, and the BMI was calculated using recorded heights and highest weights during gestation. The highest systolic blood pressure during pregnancy was compared to the average third trimester systolic blood pressure in a normal pregnancy (106 mmHg) *(7)*. Limited data were available for GCT and OGTT results, units of insulin required to normalize blood glucose during pregnancy, and the presence of acanthosis nigricans.

The impact of A1C was examined by dividing the women a priori into groups of A1C <5.1, 5.1–5.3, 5.4–5.6, 5.7–5.9, and >5.9. Fully 50% of the women had an A1C of 5.4 or higher. Those with A1c > 5.4 also had fasting glucose values >95 mg/dL.

Of the 92 women, 39 had an A1C greater or equal 5.3% and 44 had an A1C less than 5.3%. The level of 5.3% is greater than 2 standard deviations above the normal mean A1C. It was also hypothesized that this value may be a break point for distinguishing between gestational diabetes and a more severe, earlier onset glucose intolerance or undiagnosed type 2 diabetes. Thus, values higher and lower than 5.3 were grouped for further data analysis

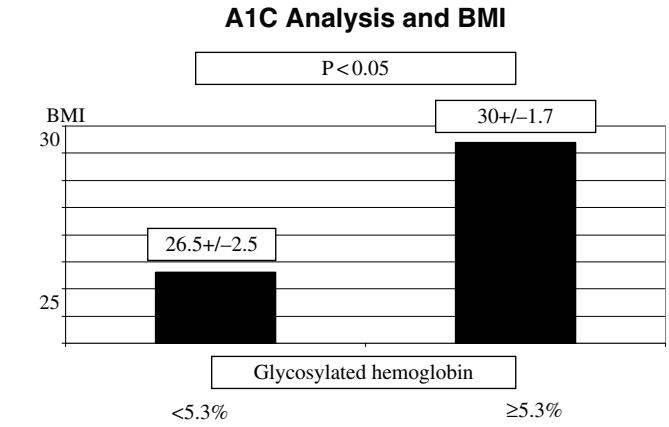


**Fig. 1.** Shows the relationship between an A1C greater or less than 5.3% and BMI ($p < 0.05$). Of the 92 women, 39 had an A1C greater or equal 5.3% and 44 had an A1C less than 5.3%. Bars are Mean+/– SD.

and showed that an A1C greater than or equal to 5.3% was correlated with a significantly higher BMI, $p < 0.001$, $r = 0.54$. (Fig. 1)

When the systolic blood pressures were examined by A1C group (less than 5.3 and greater than 5.3), it was found that the lower A1C group had an average peak systolic blood pressure of 105.4 mmHg (Fig. 2). This value is lower than the average third trimester systolic blood pressure in a normal pregnancy, which is 106 mmHg *(7)* The high A1C group, however, had an average peak systolic blood pressure of 112 mmHg, well above the normal value.

The County System utilizes the ADA protocol to administer the GCT at 24–28 wk gestation. Thus the first GCT available for analysis was the second trimester result. In the analyses of the peak postprandial glucose concentration on the GCT and OGTT results was found that the 50 g glucose challenge test corresponded with A1C values with an R-squared value of 0.8801, $p < 0.001$. Thus, the blood glucose on the GCT was an accurate predictor of A1C, which represents glucose levels for the past 2–3 mo. The elevated A1C indicated glucose intolerance long before the test was given during weeks 24–28 of gestation, and therefore before the onset of gestational diabetes, which develops around week 20. The OGTT showed a less significant correlation with A1C ($p < 0.01$, $r = 0.62$), perhaps owing to the nonlinearity of glucose response with an increasing glucose load. This observation that the GCT was associated with the A1C may be because the 100 gram glucose tolerance test

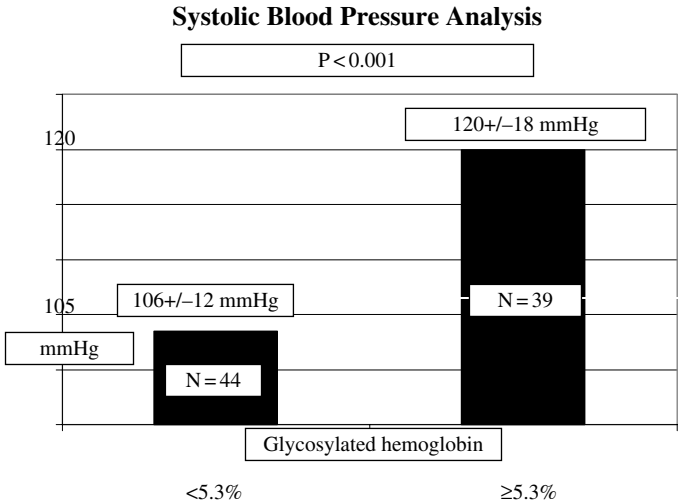


**Fig. 2.** Reveals the relationship between A1C and blood pressure, which is also significant based on a $p$-value <0.001. Of the 92 women, 39 had an A1C greater or equal 5.3% and 44 had an A1C less than 5.3%. Bars are Mean+/– SD.

does not provide a linear relationship with blood glucose compared to the peak glucose level on the 50 g glucose challenge test. (data not published).

To calculate the prevalence of women with more severe glucose intolerance, the 3 parameters of A1C, BMI, and blood pressure were used. If a woman had an A1C greater than 5.3, a systolic blood pressure greater than 106 mmHg, and a BMI of 30 or higher, she was placed into a category of more severe diabetes (whether it be type 2 or early onset GDM). Of the 51 women with complete data sets, 19 met all 3 criteria. Thus, the prevalence of more severe glucose intolerance in pregnant Mexican American women of Santa Barbara County is 37.3%. In support of this finding, the reports from a Japanese cohort showed a similar result of 40.6%, who should be classified as patients with type 2 diabetes *(5,6)*.

## SAFETY AND EFFICACY OF INSULIN ANALOGS AND ORAL AGENTS IN PREGNANCY

Maternal glucose freely crosses the placenta. Maternal insulin does not cross the placenta unless it is bound to IgG antibody, which carries it through the placenta or insulin is forced through the placenta by high perfusion *(15,16)*. Diabetic fetopathy is thought to be the result of fetal hyperinsulinemia *(15–19)*. Thus treatment must be designed to normalize maternal blood glucose concentrations without the use of exogenous insulins that cross the placenta.

Placental transfer of insulin complexed with immunoglobulin has also been associated with fetal macrosomia in mothers with near-normal glycemic control during gestation. Menon and colleagues reported that antibody-bound insulin transferred to the fetus was proportional to the concentration of antibody-bound insulin measured in the mother *(20)*. Also, the amount of antibody-bound insulin transferred to the fetus correlated directly with macrosomia in the infant, and was independent of maternal blood glucose levels. In contrast, Jovanovic and co-workers discovered only improved glucose control, as evidenced by lower postprandial glucose excursions, but not lower insulin antibody levels, correlated with lower fetal weight *(21)*. They showed that insulin antibodies to exogenous insulin do not influence infant birth weight.

Insulin lispro has been commercially available for 10 years. Insulin lispro, an analog of human insulin, has a peak insulin action achieved within 1 h after injection and thus significantly improves the postprandial glucose levels *(22)*. Because normoglycemia is paramount in the treatment of pregnant diabetic women, the use of insulin analogs would appear beneficial in the care of these women if the safety profile can be documented.

Human and highly purified insulins are significantly less immunogenic than mixed beef-pork insulins *(23)*. Human insulin treatment has been reported to achieve improved pregnancy and infant outcome compared to using highly purified animal insulins *(21)*. In 1999, the first report of the safety and efficacy of the insulin analog, lispro (which has the amino acid sequence in the beta chain reversed at position B28, B29), was reported and shown to be more efficacious than human regular insulin to normalize the blood glucose levels in gestational diabetic women *(24)*. This insulin rapidly lowered the postprandial glucose levels, thereby decreasing the glycosylated hemoglobin levels, with fewer hypoglycemic episodes, and without increasing the anti-insulin antibody levels.

In a randomized, open-label, parallel-group, clinical trial, Jovanovic et al *(25)* studied the metabolic and immunologic effects of insulin lispro and regular human insulin combined with basal insulin in GDM, and found that during a meal test, the areas under the curve for glucose, insulin and C-peptide were significantly lower in the lispro group. Mean fasting, postprandial glucose, and glycosylated hemoglobin (A1C) levels were similar for the 2 groups. The lispro group had fewer hypoglycemic episodes. The 2 groups had similar neonatal outcomes. Insulin lispro was not detectable in cord blood when patients received continuous intravenous lispro and dextrose infusions intrapartum to assess placental transfer. However, in an in vitro perfusion study using human placentas, insulin lispro was found to across the placenta at greater than normal therapeutic concentrations, with fetal perfusate concentration of lispro reaching up to 59% of maternal concentration *(19)*. The mechanism of how the placenta handles therapeutic concentrations of lispro warrants further study.

The safety and efficacy of insulin lispro has been confirmed by others *(26,27)*. In a large clinical trial *(26)* among 213 patients who had gestational diabetes and received insulin therapy (regular insulin $n = 138$, lispro $n = 75$), there was no significant differences in maternal or fetal outcomes and no increase in adverse events using lispro, but predelivery A1C values were lower and patient satisfaction was higher for insulin lispro ($p < 0.05$).

These studies support the recommendations that those women with gestational diabetes who are not optimally managed with diet and exercise need additional therapy.

In a report on the use of glyburide in pregnancy, Langer et al *(28)* showed that the outcome of pregnancies treated with glyburide was equivalent to the outcome seen in insulin treated women. However, insulin analogs were not available for study in this report. Thus, further studies are needed to confirm that glyburide does not cross the placenta and is not associated with more maternal or neonatal complications than the insulin analogs. Metformin has proven efficacy in the treatment of polycystic ovary syndrome. The literature also suggests that metformin be continued through the first trimester because the continuation of metformin improves the spontaneous abortion rate and the outcome of pregnancy nears that seen in the general population *(29)*. However, metformin has not been shown to successfully treat type 2 diabetes in pregnancy and the drug has been shown to cross the placenta. Until there are clinical trials of the safety and utility of metformin for the treatment of type 2 diabetes in pregnancy, it should not be used.

Insulin lispro causes fewer hypoglycemic events than human regular insulin, and it attenuates the postprandial response greater than regular human insulin. Furthermore, the antibody levels in lispro insulin are not increased over those seen with regular human insulin. Insulin lispro, except with high dose insulin lispro used during placental insulin studies *(19)*, does not cross the placenta to the fetus and, therefore, may be considered a treatment option in patients with gestational diabetes.

Use of insulin lispro in pregestational diabetes is now better documented to be safe in type 1 diabetic women. Diamond and Kormas first questioned the safety of using insulin lispro during pregnancy in a letter to The New England Journal of Medicine in 1997 *(30)*. They reported on 2 patients who used insulin lispro during pregnancies and deliveries. One of these pregnancies was terminated at 20 wk gestation and the second pregnancy resulted in a seemingly healthy infant after elective cesarean delivery, but who subsequently died unexpectedly 3 wk later. Both infants were discovered to have congenital abnormalities, which led the authors to question whether insulin lispro might have teritogenic effects on the fetus, in which case it should not be used during pregnancy. The report causes concerns about insulin lispro use during pregnancy, yet it does not provide conclusive evidence that insulin lispro is responsible for the malformations of the infants mentioned above. In fact, there is sufficient reason to doubt that insulin lispro is to blame in the cases described above, because these isolated case reports were not part of a study and there was no control group. Therefore, the findings should stimulate clinical trials testing the safety of insulin lispro during pregnancy, not as evidence that it is unsafe. During the initial clinical trials testing insulin lispro, pregnant women were excluded. However, some participants became pregnant unexpectedly during the trials and 19 infants were born to these mothers who were using insulin lispro. Of these births, one child had a right dysplastic kidney but the other 18 were healthy *(31)*.

Subsequently, Wyatt et al *(18)* reported that insulin lispro is safe for the treatment of type 1 diabetic women. In this retrospective analysis of the 500 pregnancies in which the women were treated with insulin lispro before and during organogenesis, there were 27 malformed infants (5.4%). All 27 congenital anomalies occurred in those infants born to mothers who had a glycosylated hemoglobin level greater than 2 standard deviations above the mean of a normal population.

Insulin aspart recently has also been shown to be safe in pregnancy *(32–35)*.

Insulin glargine is a long-acting insulin analog approved by the FDA in 2000 for use as a "basal" insulin. Insulin glargine has a glycine substitution in the alpha chain at the 21 position and 2 arginines attached to the beta-chain terminal at position 30. It is soluble insulin and has been shown to provide peakless, sustained, predictable 24-h action. Of note, insulin glargine has a 6-fold increase in IGF-1 activity over human insulin. No results of randomized clinical trials of insulin glargine use during pregnancy are currently available. There are to date only a total of 4 letters to the editor *(36–39)* reporting 14 cases of type 1 diabetic women treated with insulin glargine during pregnancy. The glucose control varied from 5.1% to 8.9%. There were no malformations in this small number of pregnancies, but the birth weight varied from 2,000 g to 4,800 g.

Insulin detemir is another long-acting insulin analog, pending FDA approval. The mechanisms of protracted action of insulin detemir include increased hexamer stability, binding to albumin at the subcutaneous injection site and in the circulation *(40)*. The benefits of insulin detemir, such as improved glycemic control, lower within-subject variation, reduced nocturnal hypoglycemic events and no weight gain have been shown in patients with

type 1 diabetes *(41,42)*. There are no clinical studies performed using insulin detemir in pregnant women with type 1 diabetes, type 2 diabetes, or GDM. Animal reproduction studies in rabbits and rats have not revealed any differences between insulin detemir and human insulin regarding embryotoxicity and teratogenicity *(43)*.

## POTENTIAL RISKS ASSOCIATED WITH INSULIN ANALOGS

### *Insulin and IGF-1 Receptor Binding Affinity*

There are medical reasons to consider increased IGF-1 activity undesirable in pregnancy. During gestation, the female reproductive system undergoes dramatic changes to accommodate the development of the fetus. IGF-1 facilitates the implantation of the human embryo in the endometrium. Disturbance of IGF-1 functions could result in spontaneous miscarriage, preeclampsia, and defects of the embryo *(43)*. It is well known that the incidence of spontaneous miscarriage owing to malformations of the fetuses during early pregnancies is much higher in women with poorly controlled diabetes than in nondiabetic pregnancies. The mechanisms for the abortion and malformation are not completely understood. There are some factors that presumably play important roles in this process: inherited genetic abnormalities of the fetus, lack of endogenous insulin in maternal serum in the case of type 1 and type 2 diabetes, and embryotoxic effects of the diabetic serum. Some researchers suspect that altered insulin and IGF-1 serum levels are candidates to account for dysregulation of trophoblast proliferation and invasion *(40)*. In late pregnancy, the placenta produces a large amount of human placental growth hormone (hPGH) to regulate the flow of nutrients to the placenta to support fetal growth *(44)*. Like growth hormone, the effects of hPGH are mediated through IGF-1 and IGF-binding proteins. An insulin analog that has high affinity for IGF-1 receptor might influence the natural processes mediated by IGF-1. Furthermore, increased hPGH and progesterone levels also account for increased insulin resistance and reduced insulin sensitivity during the last trimester.

The actions of insulin are mediated through binding of the insulin molecules to the insulin receptors located on the membrane of the target cells. IGF-1 receptor shares structural similarity to insulin receptor. IGF-1 can bind to the insulin receptor and insulin is capable of binding to the IGF-1 receptor. However, natural insulin binds to IGF-1 receptor with 1,000-fold lower affinity than insulin binding to the insulin receptor, and insulin has a 1,000-fold lower affinity than IGF-1 for the IGF-1 receptor *(45)*. The new insulin analogs all have modifications in their amino acid sequences or post-translational modifications, such as acylation of the insulin molecules in the case of insulin detemir *(41)*. Such structural modifications sometimes lead to enhanced or reduced affinity for the insulin receptor and IGF-1 receptor. It has been reported that an insulin analog B10Asp with a single amino acid substitution of aspartic acid for histidine for residue 10 of the ß chain resulted in an increase in insulin and IGF-1 receptor affinity, and demonstrated increased tumorigenic potential in female Sprague-Dawley rats *(46)*.

Kurtzhals and co-workers *(46)* compared the metabolic and mitogenic potencies of several insulin analogs including B10Asp, insulin aspart, insulin lispro, insulin glargine, and insulin detemir to that of regular human insulin, and attempted to establish a correlation between the receptor binding affinity (to insulin receptor and IGF-1 receptor) and the metabolic and mitogenic potencies of these insulin analogs. They found that metabolic potency of insulin analogs correlated well with insulin receptor affinity, whereas mitogenic potency was generally more correlated with IGF-1 receptor affinity than with insulin receptor affinity. Insulin glargine had a 6-fold increase in IGF-1 receptor affinity and a corresponding 7-fold increase in mitogenic potency as measured in a human osteosarcoma cell line (Saos/B10) that has abundant IGF-1 receptors. The B10Asp analog had a 9- to 10-fold increase in mitogenic potency, whereas insulin aspart, insulin lispro, and insulin detemir all had similar or reduced mitogenic potencies compared with to human insulin *(46)*. However, some other studies using different cell lines have shown different results. Using differentiated cultured human skeletal cells from nondiabetic and diabetic subjects, Ciaraldi et al. reported that human insulin and insulin glargine had similar mitogenic effects as determined by thymidine uptake into DNA, and the sensitivities and potencies were greatly reduced as compared to IGF-1 (< 1% of IGF-1). These researchers concluded that in a cell system representative of the relative insulin and IGF-1 receptor expression in human skeletal muscle cells, insulin glargine and native human insulin are

comparable in receptor binding, metabolic responses, and that glargine does not display augmented mitogenic effects *(47)*.

The IGF-1 signaling pathway is involved in different stages of pregnancy, and pregnancy is sensitive to alterations in the levels of these growth regulation hormones. Therefore, it may be desirable for a clinician to choose an insulin or insulin analog with minimum IGF-1 activity while treating pregnant women with diabetes. As an example, the recently released insulin detemir has a reduced affinity for IGF-1 receptor (about 1/10 that of human insulin) *(40)*, which could be beneficial if pregnant women are susceptible to overstimulation of IGF-1 receptors. However, there are no data currently available on the use of insulin detemir during pregnancy. The efficacy and safety of this new insulin analog will need to be further assessed in pregnant women with diabetes, type 1 and type 2. Many patients with type 1 or type 2 diabetes suffer from microvascular complications such as retinopathy and nephropathy. The Diabetes Control and Complication Trial (DCCT) research group reported that pregnancy was associated with an increase in the rate of retinopathy as compared to nonpregnant women. The risk of worsening of retinopathy during pregnancy was 1.63-fold greater in the intensive treatment group, and was 2.5-fold greater in the conventional group than in a nonpregnant group. Furthermore, pregnancy is often associated with worsening of glycemic control, which is another contributing factor to the worsening of retinopathy *(48–55)*. The risk factors associated with progression of retinopathy during pregnancy include duration of diabetes, severity of retinopathy at conception, metabolic control, and coexisting hypertension *(51)*. Results from many studies have indicated that rapid improvement in glycemic control was associated with progression of retinopathy in pregnant women as well as in nonpregnant patients with diabetes *(49–52)*. More recently, it has been suggested that insulin and IGF-1 may play a role in the development and progression of retinopathy. In an oxygen-induced mouse retinopathy model, knockout of insulin and IGF-1 receptors on vascular endothelial cells protected the animals from developing retinal neovascularization, and showed a reduction of vascular mediators such as VEGF, eNOS, and endothelin-1, with the effect of insulin being most significant *(53)*.

There has been a case report that 3 pregnant women with no detected background retinopathy developed bilateral proliferative diabetic retinopathy (PDR) during their pregnancies while treated with insulin lispro *(56)*. It could not be determined whether the development of PDR was owing to rapid tightening of glycemic control or owing to the effects of insulin lispro, but it may be desirable to exercise caution if lispro is used during pregnancy in women with a high risk of progressing retinopathy. Any degree of retinopathy diagnosed during pregnancy, even mild non prolifterative retinopathy, may be at risk for progression of retinopathy *(48)*. No definite conclusions can be drawn until well-designed clinical trials are conducted, and none are yet underway, to answer these questions.

The mainstay of therapy for all women with diabetes must be to safely normalize the blood glucose concentrations. To this end the use of insulin analogues that provide the appropriate glucose profiles without an associated increase in anti-insulin antibody titers are required.

## CONCLUSION AND TREATMENT RECOMMENDATIONS

The issue of GDM versus type 2 diabetes in pregnancy is one of semantics. We have clearly observed in a large county system that the women fall into two categories, those who truly have GDM and those who were unaware of their type 2 diabetes until they became pregnant. Therefore, specific criteria need to be determined that divide the women into two categories. These criteria should stem from the parameters examined in this study, with special focus on the relation among A1C, BMI, and blood pressure. Although there are several limitations in the studies presented, the evidence supports the following clinical observations.

Level 2c, observational studies suggest that women who have an elevated BMI, a systolic blood pressure greater than 105 mmHg, evidence of acanthosis nigricans and hyperglycemia in need of insulin treatment should be classified as type 2 diabetes in pregnancy (Table 1). Level 2c also is applied to the clinical recommendations that once the diagnosis of type 2 diabetes in pregnancy is made, treatment with insulin analogs lispro and aspart along with the use of human NPH is necessary. As new observations and relationships are published, ideally the evidence will lead to improved care.

**Table 1**
**Clinical Criteria to Facilitate the Diagnosis of Type 2 Diabetes in Pregnancy**

| *Test* | *Suggested Cutoff for Diagnosis* | *Level of Evidence (7)* |
|---|---|---|
| BMI | >30 | Level C |
| Fasting on OGTT | >140 mg/dl | Level C |
| One Hour on GCT | >180 mg/dl | Level C |
| Glycohemoglobin | >5.3% | Level C |
| Acanthosis nigricans | positive | Level C |
| Evidence of retinopathy | positive | Level C |
| Need for insulin therapy | before third trimester | Level C |
| Systolic blood pressure | >120 mmHg | Level C |

OGTT = Oral glucose tolerance test with 100 grams of glucose
GCT = glucose challenge test with 50 grams of glucose

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# 23 Metabolic Complications of Polycystic Ovary Syndrome

*Tracy L. Setji and Ann J. Brown*

***CONTENTS***



**Summary**

Polycystic ovary syndrome (PCOS) affects 4–7% of reproductive-aged women and is associated with serious metabolic complications including type 2 diabetes. Forty percent of affected women have impaired glucose tolerance or type 2 diabetes by the age of forty. Evaluation of women with PCOS includes metabolic risk assessment and counseling on the prevention of diabetes through lifestyle therapies such as diet, exercise, and weight loss. In addition, weight loss may improve the reproductive and cutaneous manifestations of PCOS such as impaired ovulation and hirsutism. Insulin sensitizers such as metformin also improve ovulation and insulin sensitivity in some women with PCOS. Thus, metformin is an important treatment option in women wishing to conceive or those who have hyperglycemia. There are limited data on currently available thiazolodinediones and further research is needed to define their role in this population. Finally, though oral contraceptives are commonly used to regulate menses and decrease hyperandrogenism, there is short-term evidence suggesting that they may worsen carbohydrate metabolism in some women. The long-term effects of oral contraceptives on carbohydrate metabolism warrant further investigation.

**Key Words:** Polycystic ovary syndrome; PCOS; insulin resistance; type 2 diabetes; metabolic syndrome; cardiovascular disease; metformin; thiazolodinediones; oral contraceptives; lifestyle therapies.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting 4–7% of reproductive-aged women *(1–4)*. It is characterized by irregular menses and hyperandrogenism. PCOS is associated with reproductive complications including infertility, endometrial hyperplasia, and possibly endometrial cancer *(5,6)*, as well as cutaneous manifestations such as hirsutism, acne, and male-pattern hair loss *(7)*. Recent evidence suggests that PCOS is also associated with metabolic complications including obesity *(8)*, insulin resistance *(9)*, type 2 diabetes mellitus *(10,11)*, hypertension *(12)*, dyslipidemia *(13–17)*, metabolic syndrome *(16,17)*, and possibly nonalcoholic fatty liver disease *(18,19)* and cardiovascular disease *(20–29)*. Effective management of both the reproductive and metabolic components of PCOS is a critical goal in the treatment of PCOS.

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## DIAGNOSIS

Because PCOS is a heterogenous syndrome, the diagnostic criteria have been the subject of debate. Based on a general agreement among experts at a 1990 National Institute of Child Health and Human Development (NICHD) conference, the diagnosis of PCOS requires 1) oligo- or anovulation and 2) biochemical and/or clinical signs of hyperandrogenism, such as hirsutism, acne, or androgenic alopecia *(30)*. The NICHD criteria did not include ovarian morphology as a diagnostic criterion. However, an international consensus group has recently proposed that the definition of PCOS be broadened to include ovarian morphology *(31)*. According to the 2003 Rotterdam consensus group, the diagnosis of PCOS requires 2 of the following 3 criteria: 1) oligo- or anovulation, 2) biochemical and/or clinical signs of hyperandrogenism, and 3) polycystic ovaries documented by specified ultrasound criteria *(32)*. Thus, the Rotterdam criteria created 2 new phenotypes of PCOS: hyperandrogenic women with polycystic ovaries and normal menses, and oligo-anovulatory women with polycystic ovaries and no hyperandrogenism. There is debate regarding the usefulness of these new phenotypes in clinical and research settings *(33,34)*. While this debate continues, it is important to note that most of the research to date has used the NICHD criteria, and that ultrasound features proposed by the Rotterdam conference may not be measured in scans obtained in routine clinical practice.

The NICHD and Rotterdam definitions of PCOS both require the exclusion of other causes of menstrual irregularity and hyperandrogenism. These include late-onset congenital adrenal hyperplasia (CAH), an androgen-secreting tumor, Cushing's syndrome, hyperprolactinemia, and thyroid dysfunction. These causes can be excluded through a detailed history, physical, and supplemental labs (Table 1). Further discussion regarding the evaluation and laboratory testing of women with PCOS is provided under *Clinical and Laboratory Assessment*.

## PATHOGENESIS

The etiology of PCOS is unknown. Three main hypotheses for the pathogenesis of PCOS have been proposed: 1) hypothalamic-pituitary axis abnormalities result in abnormal secretion of gonadotropin releasing hormone (GnRH). The change in GnRH secretion results in an increase in luteinizing hormone (LH), and a decrease in follicle stimulating hormone (FSH). This favors ovarian over-production of testosterone; 2) an enzymatic defect of ovarian (+/− adrenal) steroidogenesis favors excess androgen production; and 3) insulin resistance drives the metabolic and reproductive abnormalities in PCOS *(35)*. *In vitro* studies have demonstrated that hyperinsulinemia, a compensatory response to insulin resistance, stimulates ovarian theca cells from PCOS women to produce androgens *(36)*. Hyperinsulinemia also decreases hepatic sex hormone-binding globulin (SHBG) production, thus increasing bio-available testosterone *(7)*. In clinical studies, reducing hyperinsulinemia leads to a reduction in hyperandrogenemia. Based on these data, insulin resistance appears to play an important role in PCOS. Whether or not it is the primary driver for the syndrome will continue to be debated. In the meantime, the insulin resistance hypothesis provides a framework for designing therapies to address the metabolic complications of PCOS.

Both genetic and environmental factors appear to influence the phenotypic expression of PCOS. Several candidate genes have been associated with PCOS, including genes related to insulin resistance and androgen biosynthesis, transport, action and regulation *(37)*. Familial studies have suggested several modes of inheritance, including autosomal dominant with variable penetrance, x-linked, monogenic, and polygenic inheritance *(37)*. Regarding environmental factors, some studies have found that the intrauterine environment may influence the development of PCOS *(38,39)*. Both intrauterine growth retardation *(38)* and high birth-weight *(39)* have been associated with PCOS. In addition, prenatal androgen exposure has been implicated in the phenotypic expression of PCOS *(40)*. The true pathogenesis probably entails the combined influence of both genetic and environmental factors.

## METABOLIC COMPLICATIONS

### *Insulin Resistance and Beta-cell Dysfunction*

Insulin resistance is common in women with PCOS. Dunaif et al. *(9)* demonstrated that both lean and obese North American women with PCOS had increased insulin resistance compared to age- and BMI-matched controls. The insulin resistance appears to be owing to a postbinding defect of insulin receptor signaling *(41–43)*.

**Table 1**
**Laboratory testing in polycystic ovary syndrome (PCOS)**

| *Lab* | *Evaluation for* | *Comment* |
|---|---|---|
| Total testosterone | Androgen-secreting tumor | Testosterone is usually normal or modestly elevated in PCOS. However, documentation of an elevated testosterone is useful when the diagnosis of PCOS is suspected but clinical symptoms of hyperandrogenism (hirsutism, acne and male-pattern hair loss) are absent.Total testosterone >200 ng/dl should prompt a work up for androgen secreting tumor.Other measures of hyperandrogenemia include free testosterone by equilibrium dialysis or bio-available testosterone. |
| Dehydroepiandrosterone-sulfate (DHEA-S) | Androgen-secreting tumor | Although modest elevations of DHEA-S are common in PCOS, greater elevations should prompt a work up for an androgen-secreting tumor. |
| a.m. 17-hydroxyprogesterone (17-OHP) | Late-onset congenital adrenal hyperplasia (CAH) | Morning 17-OHP is a screening test for late-onset (nonclassic) CAH. This disorder is caused by a partial adrenal enzyme defect that leads to impaired cortisol production, compensatory elevation in ACTH, and hyperstimulation of the adrenal androgen pathway. |
| 24-hr urine for cortisol and creatinine | Cushing's Syndrome | This test evaluates for cortisol excess, and should be considered for women with a change in menstrual pattern, later-onset hirsutism, and other signs of Cushing's Syndrome such as hypertension, supraclavicular fullness, abdominal striae, and fragile skin. |
| Prolactin | Hyperprolactinemia | Hyperprolactinemia is a relatively common cause of oligo-amenorrhea. Patients with hyperprolactinemia may also have galactorrhea. |
| Thyroid function studies | Hyper- or hypo-thyroidism | Thyroid dysfunction is a common cause of oligo-amenorrhea and should be evaluated in all women with complaints of irregular menses. |
| 2-h oral glucose tolerance test (OGTT) | Impaired glucose tolerance, type 2 diabetes | Consider this for all PCOS women with a BMI $\geq$ 25 $kg/m^2$as well as those with a family history of type 2 diabetes or other risk factors for type 2 diabetes. Serum glucose is measured before and 120 min after consumption of a 75 g oral glucose solution. Measuring insulin levels is optional. |
| Fasting lipid profile | Dyslipidemia | Evaluate for lipid abnormalities. |
| Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) | Hepatic steatosis | Elevated liver transaminases, in the absence of other causes of liver disease, may indicate nonalcoholic fatty liver disease (NAFLD). |
| Sleep study | Sleep apnea | Consider for patients who report symptoms of sleep apnea, such as snoring, interrupted breathing during sleep, daytime somnolence, dyspepsia and morning headache. |

In addition to insulin resistance, women with PCOS appear to have impaired beta-cell function *(44,45)*. In subjects with normal glucose tolerance, increased insulin secretion from the pancreatic beta cell can compensate for insulin resistance. Impaired glucose tolerance develops when the beta cell can no longer compensate for the insulin resistance. Insulin secretory patterns in obese PCOS women reveal increased secretion of insulin under basal conditions, but relatively decreased secretion of insulin following meals *(44)*. This defect is similar to that seen in patients with type 2 diabetes. Further, the disposition index (insulin sensitivity multiplied by acute insulin

response to glucose, measured during an intravenous glucose tolerance test) is decreased in both lean and obese women with PCOS compared to age- and weight-matched controls *(45)*. These findings suggest that the acute insulin response to glucose is not adequate for the degree of insulin resistance, which provides further evidence of impaired beta cell function.

### *Impaired Glucose Tolerance and Diabetes*

The combination of insulin resistance and beta-cell dysfunction markedly increases the risk of impaired glucose tolerance (IGT) and type 2 diabetes in women with PCOS. By the age of 40, 31–35% of women with PCOS have IGT, and 7.5–10% have type 2 diabetes *(10,11)*. PCOS women who have a family history of type 2 diabetes are at a particularly high risk of type 2 diabetes. The role of family history in the risk of developing type 2 diabetes was investigated in a relatively large cohort of PCOS women with no known history of diabetes ($n$ = 408) *(46)*. This study found IGT in 35% of women with a positive family history of diabetes (defined as type 2 diabetes in either parent), compared to 19% of women with a negative family history of type 2 diabetes. Further, previously undiagnosed type 2 diabetes was found in 7% of women with a positive family history, compared to 3% with a negative family history. In comparison, the prevalence rate of type 2 diabetes among all U.S. women age 20–54 yr is 3.4% in those with a family history of diabetes affecting either parent, and 0.6% among those with no family history of diabetes *(47)*. Thus, obtaining a thorough family history is important in assessing the risk of type 2 diabetes in PCOS patients.

Studies have also investigated changes in glucose tolerance over time in women with PCOS. Norman et al. *(48)* followed 67 PCOS women (54 with normal glucose tolerance [NGT] and 13 with IGT at baseline) for an average of 6.2 yr. Among 54 women with NGT at baseline, 9% (5/54) developed IGT and 8% (4/54) developed type 2 diabetes. In addition, of the 13 with IGT at baseline, 54% (7/13) developed type 2 diabetes during that time period. Another study, conducted over a shorter time period, found a much lower rate of conversion from IGT to type 2 diabetes *(49)*. In this study, 71 PCOS women and 23 control women were followed for almost 3 yr. Sixteen percent (16%) of PCOS women with NGT at baseline converted to IGT, and 6% of PCOS women with IGT at baseline converted to type 2 diabetes. Therefore, PCOS women should undergo periodic screening for diabetes, particularly if they are overweight (BMI > or $\geq$ 25 kg/m$^2$) *(50)*.

### *Gestational Diabetes*

Some studies have demonstrated an increased risk of gestational diabetes in women with PCOS *(51,52)*. Bjerke et al. *(51)* performed a prospective cohort study that analyzed pregnancies from 52 PCOS women and 355 non-PCOS women. Eighty-three percent (83%) of the PCOS women had conceived following treatment for infertility, whereas all of the controls conceived after assisted reproduction. They found that among all women with PCOS, there was a higher incidence of gestational diabetes (7.7% vs. 0.6%, $p<0.01$), compared to non-PCOS women. However, other studies have found no difference in rates of gestational diabetes between PCOS and non-PCOS women *(53,54)*. Although the question of whether women with PCOS are at increased risk for gestational diabetes is still being debated, it is prudent to follow metabolic parameters throughout pregnancy and to counsel patients about the possibility of gestational diabetes.

### *Obesity, Hypertension, Dyslipidemia, and the Metabolic Syndrome*

In addition to insulin resistance and diabetes, PCOS has been associated with other cardiovascular risk factors such as obesity *(8)*, hypertension *(12)*, dyslipidemia *(13–17)*, and the metabolic syndrome *(16,17)*. Though not all studies have found differences in these parameters *(55,56)*, several studies have demonstrated significant differences. Talbott et al. *(15)* compared 206 PCOS women with age-, race- and neighborhood-matched control women. They documented increases in several cardiovascular risk factors including increased BMI, waist-to-hip ratio, systolic blood pressure, low density lipoprotein (LDL) and triglycerides, and reduced high density lipoprotein (HDL) in PCOS women compared to controls. Another retrospective cohort study of 786 PCOS women and 1,060 age-matched controls reported increased hypertension, dyslipidemia, and type 2 diabetes after adjustment for BMI in PCOS women compared to controls *(14)*. Further, Dejager et al. *(57)* demonstrated that PCOS women have smaller, denser LDL (thus more atherogenic) particles than age- and BMI-matched controls.

Two recent retrospective chart reviews have analyzed the presence of metabolic syndrome in women with PCOS. Apridonidze et al. *(16)* evaluated 161 PCOS women and found that BMI was >32 kg/m$^2$ in 67%, HDL <50 mg/dL in 68%, triglycerides ≥150 mg/dL in 35%, blood pressure ≥130/85 mmHg in 45%, and criteria for metabolic syndrome were met in 43%. In another study of 394 women with PCOS, Ehrmann et al. *(17)* documented waist circumference >88 cm in 80%, HDL <50 mg/dl in 66%, triglycerides ≥150 mg/dL in 32%, blood pressure >130/85 mmHg in 21%, and 33% met criteria for metabolic syndrome. Increased rates of metabolic syndrome are even seen in adolescents with PCOS in the United States (37% of PCOS adolescents vs. 5% of NHANES III adolescents) *(58)*. Based on the results of these studies, screening PCOS women for hypertension, dyslipidemia, and other features of the metabolic syndrome is recommended.

### *Cardiovascular Disease*

Several surrogate markers for cardiovascular disease are abnormal in women with PCOS, suggesting a high-risk cardiovascular profile in this group. Increased C-reactive protein (CRP) *(20–23)*, plasminogen-activator inhibitor type 1 (PAI-1) *(24,25)*, and homocysteine *(26)* have all been documented in women with PCOS. Other studies have demonstrated increased carotid artery intima media thickness *(27)* and coronary artery calcification *(28,29)* in PCOS women compared to age- and BMI-matched controls.

Although there have been several studies evaluating risk factors for cardiovascular disease in women with PCOS, there are little data on actual cardiovascular events. The presence of increased cardiovascular risk factors suggests that women with PCOS are at increased risk of cardiovascular-related morbidity and mortality, but further investigation is needed with large, prospective, long-term trials using event-related outcomes.

### *Fatty Liver Disease*

Evidence from retrospective studies suggests that women with PCOS may be at increased risk of nonalcoholic fatty liver disease. Schwimmer et al. *(18)* provided evidence that abnormal aminotransferase activity, defined as an alanine aminotransferase (ALT) >35 U/L or aspartate aminotransferase (AST) >40 U/L, was present in 21/70 (30%) of women with PCOS evaluated at an infertility clinic. Our group found that 15% (29/200) of the PCOS women in our university endocrinology clinic had an ALT or AST >60 U/L *(19)*, and 28% met the lower ALT or AST criteria used by Schwimmer et al. Moreover, the prevalence of unexplained abnormal aminotransferase activity reported in both of these studies is much higher than has been reported in a study among women in the NHANES database (4.6%), which defined abnormal aminotransfersase values as ALT and/or AST >31 U/L *(59)*. Furthermore, 6 women (mean age 29 yr) with persistently elevated aminotransferases in our study underwent biopsy, and all had evidence of nonalcoholic steatohepatitis (NASH) with fibrosis *(19)*. Therefore, evaluation for fatty liver disease in women with PCOS may be warranted at an earlier age than has been recommended for the general population.

### *Sleep disorders*

Recently, sleep disorders such as obstructive sleep apnea have been recognized in women with PCOS *(60)*. One study comparing 53 women with PCOS to 452 premenopausal female controls found that women with PCOS had increased sleep disordered breathing (17.0% vs. 0.6%, $p < 0.001$) and excessive daytime sleepiness compared to controls (80.4% vs. 27.0%, $p < 0.001$). Interpretation of this study is limited because the controls were not matched for BMI. However, comparing subjects with a BMI >32.3 kg/m$^2$, 8/41 (19.5%) of PCOS women and 3/66 (4.5%) of controls had sleep apnea. Further, insulin resistance, assessed by fasting plasma insulin levels and glucose to insulin ratios obtained during an OGTT, was a greater risk factor than BMI for sleep disordered breathing in this study.

## CLINICAL AND LABORATORY ASSESSMENT

A detailed patient history and physical exam focusing on menstrual history and signs of hyperandrogenism frequently provide enough information to make a presumptive diagnosis of PCOS. PCOS is typically characterized by a long history of irregular menses, with the onset at puberty, and slowly progressive hyperandrogenism. Abrupt changes in menses or hyperandrogenism symptoms are not usually seen and should serve as an indication

to evaluate for other causes. For instance, rapid progression of hirsutism should prompt an evaluation for an androgen secreting tumor or Cushing's syndrome. A change in menstruation from a regular ovulatory pattern to an irregular pattern should also prompt an evaluation for these diagnoses, as well as hyperprolactinemia and thyroid dysfunction. Screening for congenital adrenal hyperplasia can be reserved for women at relatively greater risk for this uncommon disorder, such as those with Ashkenazi Jewish ethnicity, for whom the prevalence is estimated to be 3–4% *(61)*. Lab testing can be used to exclude these other potential causes of irregular menses and/or hyperandrogenism (Table 1).

Lab testing can also be used to establish the diagnosis in women with mild or no clinical evidence of hyperandrogenism, but other features suggestive of PCOS. In this case, documentation of hyperandrogenemia (elevated testosterone levels) combined with oligo-ovulation and/or ultrasound evidence of polycystic ovaries provides the diagnosis.

Once the diagnosis is established, evaluation for metabolic complications should be considered for all PCOS women. Because postprandial glucose is elevated before fasting hyperglycemia develops, an oral glucose tolerance test (OGTT) is useful in detecting abnormal glucose metabolism in its early stages. Thus, an OGTT is recommended to assess glucose tolerance in women with PCOS *(62)*, particularly if they have a BMI $\geq$25 kg/m$^2$ *(50)* or have a first degree relative with type 2 diabetes *(46)*. Aminotransferases and a fasting lipid profile will screen for fatty liver and dyslipidemia, respectively. In patients with sleep apnea symptoms, referral for a sleep study may be indicated. Table 1 summarizes laboratory testing for the most common metabolic abnormalities seen in PCOS and for distinguishing PCOS from other disorders.

## TREATMENT

### *Lifestyle Interventions*

Lifestyle interventions are the cornerstone of PCOS therapy, particularly for the prevention and treatment of metabolic disease. Nonrandomized trials have shown that a reduction in body weight by approximately 15% through dietary modification alone improves insulin sensitivity *(63,64)*, decreases androgen levels *(63,65)*, and increases ovulatory frequency *(64,65)*. Studies with smaller weight loss have provided less impressive results. Kiddy et al. *(66)* documented improvement in insulin sensitivity, free testosterone levels, and menstrual function in PCOS women who lost more than 5% of their body weight, but not in those who lost less than 5%. Two small randomized trials evaluating the effects of a high protein versus low protein diet in PCOS women found that subjects in both groups had improvements in fasting insulin and area under the curve (AUC) for insulin measured during an OGTT, but documented no difference among the diets on these parameters *(67,68)*. However, there were minor improvements in HDL, TC/HDL, area under the curve (AUC) for glucose measured during an OGTT, and free androgen index in the high protein group compared to the high carbohydrate group in one of the studies *(67)*.

Studies evaluating the effects of weight loss through a combination of diet and exercise in women with PCOS have also been nonrandomized trials. Huber-Buchholz et al. *(69)* demonstrated that a 6-mo diet and exercise program, resulting in a mean weight loss of 2–5% in 18 infertile, overweight PCOS women, improved insulin sensitivity and ovulation in some, but not all of the subjects. Clark et al. *(70)* documented improvement in fasting insulin, testosterone levels, ovulation, and fertility in 13 obese PCOS women who successfully completed a 6-mo diet and exercise program. These same investigators subsequently conducted a prospective 6-mo diet and exercise trial in 87 anovulatory, infertile PCOS women *(71)*. Sixty-seven of the subjects completed the program and lost an average of 10.2 kg. Of these 67 women, 60 resumed spontaneous ovulation, 52 achieved pregnancies, and 45 gave birth. The rate of miscarriage decreased from 75% before the program to 18% upon completion of the program. More recently, Crosignani et al. *(72)* demonstrated that in PCOS women who lost 5% and 10% of their body weight through diet and exercise, there was an 18% and 27% reduction in ovarian volume, respectively, and a reduction in the number of microfollicles. It has been hypothesized that a reduction in ovarian volume and number of microfollicles may result in decreased production of androstenedione and subsequent improvement of PCOS symptoms.

The only study of exercise alone (without dietary changes or weight loss) in women with PCOS is an observational trial that evaluated the effects of 6 mo of brisk walking. Twelve of the 21 women adhered to the

program; plasma total homocysteine levels decreased in those women. There was no change in fasting insulin levels in either group *(73)*.

To summarize, small trials have suggested that lifestyle therapies improve insulin sensitivity and ovulation in PCOS, particularly when weight loss is >5% of initial weight. However, there have been no large randomized, controlled trials in women with PCOS to confirm these findings. Nonetheless, studies of other populations at high risk for diabetes, such as the Diabetes Prevention Program, have shown that in men and women with impaired glucose tolerance, intensive lifestyle therapy resulting in a weight loss of 5–7% decreases the conversion to type 2 diabetes by 58% over a 3 yr period *(74)*. Therefore, lifestyle therapies including diet, exercise, and weight loss (if overweight or obese) are recommended in women with PCOS.

### *Metformin*

Metformin inhibits the production of hepatic glucose and increases insulin sensitivity. In clinical trials, it has been shown to decrease risk of conversion from IGT to type 2 diabetes in middle aged adults by 31% over 3 yr *(74)*. This finding has made metformin a potentially attractive therapy for diabetes prevention in other populations, including those with PCOS.

Velazquez et al. *(75)* were the first to report improvement in insulin sensitivity and androgen levels in PCOS women treated with metformin. This uncontrolled study also had the unexpected findings of normalization of menses and spontaneous pregnancies in some of the subjects. Subsequent randomized controlled trials confirmed these effects of metformin on insulin resistance, ovulation, and androgen levels. Moghetti et al. *(76)* conducted a randomized controlled trial of metformin 500 mg 3 times daily vs. placebo for 6 mo in 23 PCOS subjects. They found significant improvements in insulin sensitivity measured by the hyperinsulinemic euglycemic clamp, serum free testosterone, and menstrual function (with normalization of cycles in 50% of the subjects). Fleming et al. *(77)* conducted a larger randomized controlled trial that used a smaller dose of metformin. In this trial, women with oligomenorrhea and polycystic ovaries were randomized to 14 wk of metformin 850 mg per day *(45)* versus placebo *(48)*. Although the study was limited by a large number of dropouts in the metformin group (15/45 in the metformin group vs. 5/47 in the placebo group), it demonstrated significant improvement in ovulation in the metformin group compared to placebo (23% vs. 13%, $p < 0.05$). The authors did not find a significant difference in fasting or 2-h insulin levels among the groups.

In 2003, a Cochrane database meta-analysis of metformin therapy in PCOS was published, which included 13 trials and a total of 543 participants *(78)*. The authors concluded that metformin was an effective treatment for anovulation in PCOS. They reported an odds ratio of 3.88 (95% confidence interval [CI] 2.25–6.69) and achievement of ovulation in 46% of those who received metformin versus 24% of those who received placebo. Although there is some evidence that metformin increases ovulatory frequency in nonobese women with PCOS *(79)*, the 2 trials with the lowest body weight in the Cochrane review did not show improved ovulation with metformin *(78)*. The addition of metformin to clomiphene-citrate appears particularly effective at inducing ovulation, with an odds ratio of 4.41 (95% CI 2.37 to 8.22) compared to clomiphene alone, with ovulation rates of 76% vs. 42%, respectively *(78)*. Whether this improvement in ovulation translates to improved live birth rates is not clear. A recent large randomized controlled trial of 626 infertile PCOS women demonstrated a live birth rate of only 7.2% of those randomized to clomiphene alone, and 26.8% of those randomized to combination theraphy with clomiphene and metformin.

Additional benefits of metformin therapy reported in the Cochrane review included reduction in fasting insulin levels, blood pressure (in an analysis of 47 subjects) and LDL cholesterol (in an analysis of 97 subjects) *(78)*. Although the authors found a significant effect of metformin on androgen levels when all of the studies were analyzed, this effect was no longer significant once 2 trials that reported very large treatment effects were excluded. They did not find evidence that metformin had an effect on body mass index or waist to hip ratio.

Since the Cochrane database review was published, Tang et al. *(81)* reported results from a randomized, double-blind, placebo-controlled trial in which PCOS women were randomized to 6 mo of metformin 850 mg twice daily ($n = 69$) or placebo ($n = 74$). These investigators found a significant decrease in the free androgen index, but no difference in menstrual frequency or insulin sensitivity in those treated with metformin compared to placebo. However, both groups lost weight (3.98% in metformin group, 4.41% in placebo group, $p = 0.554$). This weight loss was associated with a significant improvement in menstrual function, but not improvement in insulin

sensitivity as measured by the Quantitative Insulin Sensitivity Check Index (QUICKI). The authors speculate that the lack of improvement in insulin sensitivity may be owing to the high initial BMI of the subjects (37.6 kg/m$^2$ in metformin group, 38.9 kg/m$^2$ in placebo group) and/or an insufficient dose of metformin. They are currently conducting a metformin dose-finding trial to answer this question.

Though metformin can induce ovulation in some women with PCOS, its continued use during pregnancy is controversial. There is evidence from observational studies *(82,83)* and a recent randomized controlled trial that metformin decreases spontaneous abortion rates *(84)*. In addition, metformin may reduce the incidence of gestational diabetes in PCOS women *(83)*. However, metformin is currently category B and further studies are needed to document its safety during pregnancy.

The above data provide evidence that metformin can improve insulin sensitivity in women with PCOS, though it is possible that very obese women may experience less of an effect or require a larger dose of metformin. In addition, metformin may decrease androgen levels, but data are controversial. Metformin appears to be an effective mode of enhancing ovulation, particularly in combination with clomiphene-citrate, in women with PCOS. However, results from a large randomized multicenter trial comparing the effects of metfromin vs. clomiphene vs. combination therapy with both metformin and clomiphene on live birth rates do not support the superiority of combination therapy *(80)*. It is important to note that not all women will respond to metformin with increased menstrual frequency and ovulation. Currently, we are not able to predict who will respond, though there is some evidence that baseline insulin resistance is a predictor *(76)*. Because fertility may improve with use of metformin, any patients who do not wish to become pregnant should be counseled about contraception.

### *Thiazolodinediones*

Thiazolodinediones increase liver, skeletal muscle, and adipose tissue insulin sensitivity. Azziz et al. *(85)* conducted a randomized, double-blind, placebo-controlled trial evaluating the effects of troglitazone (600 mg/d, 300 mg/d, and 150 mg/d) vs. placebo in women with PCOS. The investigators reported dose-related improvement in ovulatory rates, hirsutism, free testosterone, sex hormone-binding globulin levels, and measures of insulin resistance assessed by a 2-h glucose tolerance test. For instance, ovulation occurred over 50% of the time in 42% and 57% of patients on 300 mg/d and 600 mg/d, respectively, compared to 12% of patients on placebo. Of note, there were small but significant increases in body mass in both the 300 mg/d and 600 mg/d troglitazone groups (+0.78 kg and +1.01 kg, respectively). These investigators found favorable trends but no significant response of any lipid parameters *(86)*. Although there was no difference in the proportion of subjects who experienced aminotransferase elevations in this study, troglitazone was withdrawn from the market in 2002 secondary to hepatic toxicity.

Subsequent small trials evaluating the effects of rosiglitazone and pioglitazone also report benefits in PCOS women. Uncontrolled trials have demonstrated improvements in insulin sensitivity and ovulatory frequency with rosiglitazone alone *(87–89)* or in combination with clomiphene-citrate *(88)*. A recent randomized controlled trial of 30 PCOS women confirmed these findings and reported improvement in hyperandrogenemia *(90)*. Additionally, a randomized, controlled trial documented significant improvements in insulin sensitivity and ovulation as well as hyperandrogenemia in women with PCOS treated with pioglitazone (30 mg/d) for 3 mo compared to placebo *(91)*.

There have been 3 randomized trials comparing effects of thiazolodinediones and metformin *(92–94)*. Ortega-Gonzalez et al. *(92)* randomized 52 obese PCOS women to either pioglitazone (30 mg/d) or metformin (850 mg 3 times daily) for 6 mo. They found that both treatments resulted in improvement in free testosterone levels, hirsutism, and measures of insulin resistance assessed by a 2-h OGTT. However, the pioglitazone group had a significant weight gain of 4.7 kg whereas the metformin group had a nonsignificant 3.2 kg weight loss. This study did not assess ovulatory changes in response to therapy. Randomized trials comparing rosiglitazone to metformin in PCOS women have provided mixed results. Baillargeon et al. *(93)* found similar reductions in androgen levels, but more improvement in ovulation rates and measures of insulin resistance with metformin compared to rosiglitazone. In contrast, Rouzi et al. *(94)* reported better ovulation rates with rosiglitazone than metformin, and similar reductions in androgen levels and insulin resistance in both groups.

In summary, a large, randomized controlled trial demonstrated that troglitazone improved ovulation, androgen levels, and insulin resistance in women with PCOS, but this drug is no longer available. Small randomized placebo-controlled trials of pioglitazone and rosiglitazone, and randomized trials comparing thiazolodinediones

to metformin suggest that both therapies may improve these outcomes. However, there is currently little evidence of benefit of thiazolidinediones over metformin, especially considering the weight gain that can be seen with thiazolodinediones. Further investigation of these medications is warranted. Because thiazolidinediones do appear to increase ovulatory frequency in some women with PCOS, patients initiating thiazolidinedione therapy should be counseled to use contraception. Thiazolodinediones are currently category C drugs, and further studies are needed to determine safety during pregnancy.

### *Hormonal Contraceptive Therapy (Oral Contraceptives, Patches, or Rings)*

If fertility is not an immediate goal, estrogen-progestin therapy can be used to treat oligoamenorrhea and symptoms of hyperandrogenism. Cyclic estrogen-progestin therapy induces regular withdrawal bleeding, and prevents endometrial hyperplasia. By suppressing pituitary LH secretion, estrogen-progestin therapy reduces ovarian androgen production, and reduces symptoms of androgen excess. In addition, estrogen increases hepatic production of sex-hormone binding globulin, which reduces bio-available testosterone. Thus, hormonal contraceptive therapy treats many components of PCOS by providing endometrial protection, cycle control, contraception, and cosmetic improvement in hirsutism and acne. *(95,96)*.

A potential adverse effect of oral contraceptive therapy is worsening of insulin resistance and carbohydrate metabolism *(97)*. Trials evaluating the metabolic effects of oral contraceptive therapy in PCOS women have demonstrated conflicting results *(98–100)*, which has led to some controversy over their use in this population *(100)*. However, most trials to date have had relatively small sample sizes, short-term outcomes, and often lack a placebo group. The potential metabolic risks of hormonal contraceptive therapy are important caveats to therapy. But until potential risks are further clarified, hormonal contraceptive therapy is an effective way to treat many of the symptoms of PCOS and to prevent endometrial hyperplasia. Further investigation of the long-term effects of oral contraceptive therapy on carbohydrate metabolism is warranted.

In addition to effects on insulin resistance, the estrogen component of hormonal contraceptive therapies can increase blood pressure. Thus, blood pressure should be monitored upon initiation of estrogen-containing therapies. In women with hypertension, or those who smoke, estrogen-containing contraceptive therapies are relatively contraindicated. A progestin-only contraceptive agent, such as norethindrone 0.35 mg daily, may be safer. This will provide contraception and cycle control, but will not treat hirsutism or acne.

### *Anti-Androgen Therapy (spironolactone, flutamide, finasteride)*

Spironolactone, which has antiandrogenic action, is an effective method of treating hirsutism *(102)*. The ability to reduce hirsutism by spironolactone appears to be similar to that of flutamide *(103)* and of finasteride *(104)*. Flutamide is a nonsteroidal anti-androgen used to treat prostate cancer. Although small studies have shown potential benefit in PCOS *(103–106)*, flutamide's use in healthy women with PCOS is limited by risk of hepatic dysfunction. Finasteride blocks the conversion of testosterone to di-hydrotestosterone at the hair follicle. Its use is limited secondary to possible fetal effects (category **X**). Because each drug is similarly effective in treating hirsutism, spironolactone is generally preferred because of its safety profile. However, each drug is contraindicated during pregnancy because of potential teratogenicity.

### *Other Treatments*

There have been small trials evaluating diazoxide *(107)*, orlistat *(108)*, acarbose *(109)*, and D-*chiro*-inositol *(110)* that report potential benefit in PCOS women. Larger trials are needed to confirm these benefits before their use is recommended in this population. Topical therapies to reduce facial hair growth (enflornithine hydrochloride 13.9% cream), or stimulate scalp hair growth (minoxidil 2% or 5%) may also be useful.

## SUMMARY

PCOS is the most common endocrine disorder in reproductive-aged women. In addition to reproductive and cutaneous manifestations, several studies have documented increased risk of serious metabolic complications in women with PCOS, most notably insulin resistance and type 2 diabetes. The clinical evaluation of women

Table 2
Suggested clinical framework for addressing both metabolic and reproductive issues: "MY PCOS" *

| | |
|---|---|
| **M**etabolic | Assess diabetes mellitus and cardiovascular disease risk<br>Assess risk of nonalcoholic fatty liver disease<br>Address lifestyle therapies, such as nutrition, activity and stress management |
| C**y**cle Control | Assess bleeding pattern and risk for endometrial hyperplasia<br>Provide therapies to prevent endometrial hyperplasia<br>Hormonal contraception (oral contraceptive, vaginal ring, patch)<br>Cyclic progesterone withdrawal (every 1–3 mo) |
| **P**sychosocial | Address body image<br>Discuss eating behaviors<br>Screen for depression<br>Discuss stress management<br>Provide nonjudgmental support |
| **C**osmetic | Discuss use of estrogen-containing contraceptives to suppress androgens<br>Consider spironolactone 50-100 mg twice daily for refractory hirsutism or acne.<br>Discuss enflornithine hydrochloride cream, laser therapy and electrolysis.<br>Suggest topical minoxidil for male-pattern scalp hair loss |
| **O**vulation | Discuss fertility goals<br>Discuss therapies to increase ovulation frequency<br>Weight loss<br>Metformin<br>Consider referral to Reproductive Endocrinology for assisted reproductive technologies |
| **S**leep Apnea | Screen for sleep apnea (interrupted breathing while asleep, snoring, morning headaches, heartburn, daytime somnolence)<br>Refer for sleep study if indicated |

*This acronym was developed by the authors for use in their Duke PCOS clinic and to aid in resident teaching.

with PCOS should be comprehensive (see Table 2 for our recommended approach) and include a thorough risk assessment for these metabolic complications. Treatment of women with PCOS should emphasize prevention of diabetes and cardiovascular disease through lifestyle therapies (see Table 3 for levels of evidence of therapeutic recommendations in PCOS). Furthermore, weight loss through diet and exercise appears to improve ovulation and hyperandrogenism in women with PCOS. Pharmacological therapy with insulin sensitizers has also been studied in women with PCOS. Metformin appears to improve ovulation and insulin sensitivity in some women with PCOS. Although troglitazone resulted in improvement of insulin sensitivity, hyperandrogenism and ovulation in women with PCOS, the thiazolodinediones currently available have less evidence to support their use in this population. Hormonal contraceptive therapy can effectively regulate menstrual cycles and treat symptoms of

Table 3
Level of evidence for prevention of type 2 diabetes and improvement of ovulation in PCOS

| *Treatment* | *Indication* | *Level of Evidence* |
|---|---|---|
| Lifestyle therapies (diet, exercise and weight loss) | Prevention of type 2 diabetes | Grade 1C+ |
| | Improve ovulation | Grade 1C+ |
| Metformin | Prevention of type 2 diabetes | Grade 1C+ |
| | Improve ovulation | Grade 1B |
| Rosiglitazone/Pioglitazone | Prevention of type 2 diabetes | Grade 2C |
| | Improve ovulation | Grade 2B |

hyperandrogenism, but may possibly cause deterioration in carbohydrate metabolism. Further studies are needed to better characterize the long-term metabolic complications as well as the effects of the above medications on these complications in women with PCOS.

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# 24 Erectile Dysfunction in Diabetes

*Andrew J. M. Boulton*

***CONTENTS***



## INTRODUCTION

Erectile dysfunction (ED) is defined as "the persistent inability to attain or maintain an erection sufficient for sexual intercourse" *(1)*. It is the commonest sexual dysfunction in men, is increasingly common with aging, may affect up to 10% of the nondiabetic male adult population, and is even more common among patients with diabetes. It may be defined as primary, in which cases there has never been normal sexual function, or secondary, which occurs after a period of normal sexual function: ED in diabetes is invariably secondary.

Major changes in the management of ED have occurred in the last 10 yr. As recently as 1998, a review reported that most men with ED were treated with injection therapy and vacuum pumps: the authors lamented the lack of an "on-demand," rapidly acting, safe, and effective oral therapy *(2)*. The development of selective inhibitors of cyclic guanosine monophosphate (c-GMP)-specific phosphodiesterase type 5 (PDE-5) revolutionized the management of ED such that the majority of diabetic men with ED can now be treated effectively with oral medication *(3–5)*.

In this chapter a discussion of the physiology of the normal erection will be followed by a description of the multifactorial etiology of ED in diabetes. The prevalence, clinical evaluation, and modern management of ED in diabetes will conclude this chapter.

### *Epidemiology of Erectile Dysfunction in Diabetes*

It is estimated that over 10% of the nondiabetic population in the United States has ED, and that 1 in 3 men will experience the problem at some time. Longitudinal data from the Massachusetts male aging study showed significant changes in erection frequency, sexual intercourse, desire, and satisfaction in middle aged men during a nine-year follow-up *(6)*. The within-person change in all three of these outcomes strongly related to age, with decline in sexual function becoming more pronounced with increasing age. In diabetes, this process appears to be exaggerated. Overall prevalence of ED among diabetic men in hospital clinic populations is probably between 30 and 50% *(7,8)*. As in those without diabetes, the prevalence increases with age, but is generally lower in those with type 1 diabetes at about 20% *(9)*. Data from primary care are similar; demonstrating a prevalence of 55% among diabetic men, of whom nearly 40% reported that the problem was persistent *(10)*.

The same primary care study reported on the impact of ED on quality of life (QOL): nearly half of ED sufferers frequently thought about their ED, with a significant majority reporting that ED severely impacted on

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their QOL *(10)*. More recently de Beradis et al *(11)* showed that males with type 2 diabetes and ED are prone to poor QOL, worsening physical function, social function, general health, and increased depressive symptoms.

It is clear therefore from these and many other studies that ED is a serious and frequent complication of diabetes that adversely impacts not only patients but also their partners. It is important to ask all male patients at least annually whether they experience symptoms of ED *(12)*.

## *Normal Erectile Function and Pathophysiology of Erectile Dysfunction*

Normal sexual function is characterised by libido (sexual interest and desire), sexual activity, and spontaneous, usually nocturnal, erections. A normal erection is predominantly a vascular event that depends upon the coordinated function of a number of psychological, neurological, hormonal, and vascular systems.

Sexual stimulation results in an increase in parasympathetic nervous activity leading to a relaxation of the cavernosal smooth muscle, compression of the outflow venules against the tunica albuginea with resultant engorgement of erectile tissue *(1)* (Fig. 1). It is now clear that nitric oxide (NO) is the major chemical mediator resulting in relaxation of smooth muscle cells in the erectile tissue, thus allowing the erection to occur. Nitric oxide release results in the release of cyclic GMP (cGMP), which is broken down by PDE-5 (Fig. 1). The PDE-5 inhibitors prevent breakdown of cGMP thereby enhancing erection under situations of normal sexual stimulation.

## *Etiology of Erectile Dysfunction in Diabetes*

The etiology of ED in men with diabetes is invariably multifactorial: as can be seen in Fig. 1, there are potential pathologies that may interrupt the pathway to a normal erection. Most important among these are diabetic neuropathy, vascular disease, including hypertension, psychogenic factors, personal habits including smoking and alcohol intake, and concomitant medication. Experience and evidence suggests however that the most common factors in diabetes are autonomic neuropathy and endothelial dysfunction. Some years ago, a study of corpus

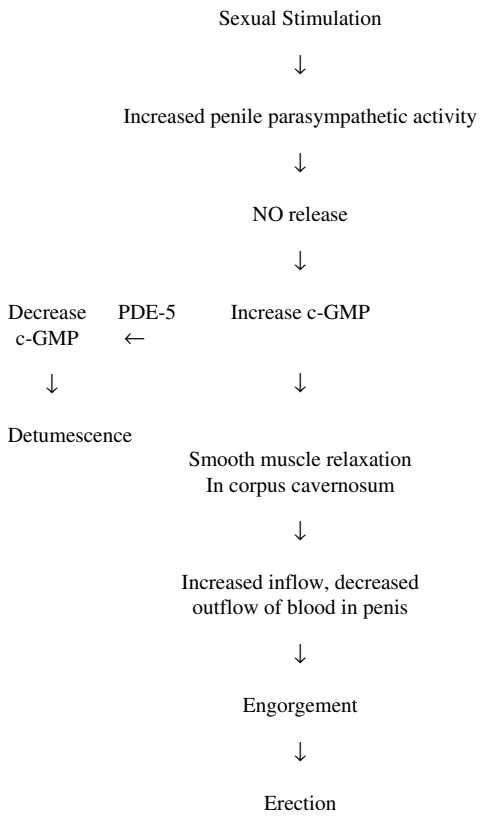


**Fig. 1.** Physiology of normal erection.

**Table 1**
**Medications association with erectile dysfunction**

| *Antihypertensives* | *Related to nervous system* |
|---|---|
| Thiazide diuretics | Phenothiazines |
| Beta-blockers | Tricycle antidepressants |
| Spironolactone | Tranquillizers |
| Methyl-dopa | |
| *Endocrine* | *Others* |
| Estrogens | Antifungals |
| Antiandrogens | Metoclopramide |
| Steroids | Clofibrate |
| | Gemfibrozil |
| | Antihistamines |

cavernosal tissue from diabetic men showed that there was a failure of NO mediated smooth muscle relaxation owing to a combination of neuropathy and endothelial dysfunction *(13)*.

A study from the UK assessed causes of ED in 110 diabetic men presenting to a diabetes ED clinic *(14)*: neuropathy was most common, present in 65% of all patients, but psychogenic factors were deemed to be contributory in over 50% of cases. Significantly, medication usage, particularly of antihypertensives, was contributory in 25% of cases: Table 1 lists common medications that might cause ED, many of which are used with increased frequency and in combination among patients with diabetes. The rather low prevalence of vascular disease in the study of Veves et al *(14)* may reflect referral bias to that clinic, which is known to have an interest in neuropathy.

Smoking and alcohol are also well recognized risk factors for ED: a recent study showed that the risk of ED increased with smoking and that men with ED were more likely to start smoking *(15)*. In summary, several risk factors usually interact and result in ED in men with diabetes

## INVESTIGATION OF ERECTILE DYSFUNCTION IN DIABETES

In most cases of ED in diabetic men, a history and careful clinical examination is all that is required, with few investigations being necessary; with the development of new and effective oral treatments for ED, investigation and management is much simplified and in many cases rewarding.

### *History*

A detailed sexual history is essential in all cases, particularly relating to the mode of onset of ED, the presence or absence of nocturnal erections, and a history of previous normal sexual function. The patient with a gradual onset of ED that was initially intermittent and associated with loss of morning erections strongly suggests an organic cause. Conversely, a psychogenic cause may be characterized by ED of sudden onset with the preservation of nocturnal erections. However, most patients have a multifactorial etiology, so that the causation may not be clear cut from the history. The physician should enquire for the presence of symptoms of peripheral and autonomic neuropathy as well as peripheral vascular disease. A careful social history of smoking and alcohol intake and an enquiry as to what medications a patient is taking are also essential.

### *Examination*

Particular attention should be paid to the lower extremities, as evidence of peripheral neuropathy or vascular disease is particularly relevant. The genitalia should be examined to exclude penile abnormalities such as Peyronie's disease and testicular atrophy.

### *Psychosexual History*

A psychosexual evaluation can be made by the diabetes physician, but if available, a qualified sex therapist or psychiatrist/psychologist with a special interest in psychosexual assessment and management can be a valuable

member of the team. A major problem in this particular area is that many physicians fail to document the history appropriately because of the physician's and patient's discomfort with sexually explicit questions. This is particularly regrettable because a careful history taken with sensitivity can on its own, in many cases, lead to the correct diagnosis.

### *Investigations*

Most practitioners consider that at a minimum serum testosterone and prolactin should be assessed in all men with diabetes and erectile dysfunction. However, this remains controversial *(16)*: Veves et al demonstrated that only 1 patient out of 110 was found to have a low testosterone, FSH, and LH *(14)*. The history and examination will help to determine if a hormonal etiology of the ED in a particular patient is likely.

## TREATMENT OPTIONS

A large number of options are now available for the management of ED in people with diabetes. Treatment choices will of course depend upon a number of circumstances, including the experience of the practicing physician, local availability of treatment options, and most importantly, patient preference. The treatments will be discussed in the likely order of consideration, although this may vary. Many of the studies discussed below have only considered treatments on an individual basis. However, a recent study has confirmed the benefits of using a progressive step-wise treatment program, which may combine a number of the therapies listed below *(17)*.

### *Lifestyle and Medication Management*

Before considering any form of pharmacological or physical therapies, an effort should be made to rationalize the patient's medications, especially those drugs liable to promote erectile dysfunction (Table 1). Antihypertensive agents and other drugs commonly used in patients with diabetes may well be contributory to the ED. Clearly much care and consideration must be taken when altering medications in this way. Similarly, a careful discussion with the patient about the potentials of both smoking and excessive alcohol intake to be important in the pathogenesis of ED is indicated at this juncture. Both changes in lifestyle and the medication regimen can result in the restoration of erectile function sufficient for normal intercourse in some patients *(14,15)*.

### *Psychosexual Counselling*

It has been argued that psychosexual counselling may result in increased cost and that diabetologists can provide the same service, if necessary *(18)*. However, it should of course be remembered that psychosexual counselling may require the same time or even more, from the diabetologist and that employing a specialist may be cost effective. If psychosexual counselling is to succeed, both the patient and the partner should be involved: even in cases where a number of causes have been identified the use of psychosexual counselling and techniques such as sensate focus have led to the resumption of sexual activity within the relationship *(14)*. Sexual therapy should be considered seriously for people with diabetes because the chronic nature of the disease is associated with situational stresses, performance anxiety, and problems in existing or newly formed relationships *(19)*. The optimal management of ED is best achieved by accepting treatments that address the complex interplay of biological and psychological issues involved in normal sexual behavior. Both partners should therefore be involved in discussions, choice of treatments, and all stages of management.

### *Oral Therapies*

#### PDE-5 Inhibitors

Until approx 15 yr ago, a number of oral agents had been tried in the management of ED. These included yohimbine (predominantly considered no more than an aphrodisiac) and the antidepressant Trazodone, both with few data to support their use. It was approximately 15 yr ago in the UK that a drug designed to inhibit PDE-5 was undergoing phase 1 and 2 studies as a potential antianginal agent by Pfizer. At the end of the study, investigators and the company were surprised when many trial subjects refused to return unused tablets, reporting that previous ED had resolved. This drug was later named sildenafil (Viagra) and it was the first of the PDE-5 inhibitors to be

launched. Early studies of the efficacy of sildenafil demonstrated remarkable results *(3,4)*, with up to 70% of all attempts at sexual intercourse being successful compared with approximately 20% on placebo. Early studies in diabetes also showed significant efficacy on sildenafil versus placebo *(5,20)*. The larger of these two studies from the United States *(20)* enrolled 268 men who participated in a 12-wk study. Among these, 61% reported at least one successful attempt at intercourse during the study compared to 22% on placebo. Common adverse events similar in most studies included headache, dyspepsia and sinus congestion/discharge. Several of these are probably related to the hypotensive effect of sildenafil. A later study from Europe enrolled 219 patients but in contrast to the previous US study, all patients had type 2 diabetes. Surprisingly, the results were even more impressive than in the combined type 1/type 2 study, with 65% of patients reporting improved erections on sildenafil compared with only 11% on placebo *(21)*. When the results were analysed according to glycemic control or the presence or absence of complications, the treatment was equally efficacious in those with modest or poor control and also in those without complications or with at least one microvascular complication.

A common finding in most studies of sildenafil in the management of ED was that patients with diabetes usually required 100 mg although some responded to 50 mg.

Adverse events associated with the use of sildenafil were closely monitored by regulatory authorities in the U.S. and Europe as there was particular concern about the increased risk of cardiovascular events in diabetic men who may well have underlying cardiovascular disease. It is clear that PDE-5 inhibitors are absolutely contraindicated in any patients taking nitrates by any route because of the risk of precipitous hypotension when these drugs are used in combination. It was also agreed in a consensus document, prepared jointly by the American College of Cardiology and the American Heart Association *(22)*, that the cardiovascular effects of PDE-5 inhibitors may be potentially hazardous in patients with active coronary ischemia even if not taking nitrates, in those with congestive heart failure and borderline low blood pressure, in patients on complicated multidrug and antihypertensive medications and patients taking any drug that might prolong the half-life of the PDE-5 inhibitor *(22)*.

More recently, two other PDE-5 inhibitors have been licensed for the management of ED: these are tadalafil (Cialis) and vardenafil (Levitra) Although tadalafil has a longer half life than the other two agents, the results of trials with tadalafil (10–20 mg) and vardenafil (10–20 mgs) are not dissimilar to those with sildenafil (50–100 mg) *(23,24)*. The efficacy of these three agents is compared in Table 2. Unfortunately, there have been no direct trials in which patients were randomized to one of the three PDE-5 inhibitors available. There is some suggestion in the literature that substitution of a second inhibitor may be useful when the first has failed; however, these studies have come under criticism regarding study design *(25)*. In summary the PDE-5 inhibitors appear to be highly efficacious agents for the management of ED in diabetes and a response can be expected in up to two-thirds of all diabetic men whatever the cause of their ED. The side-effect profile and contraindications are similar among these three agents (Table 2): all are contraindicated in patients taking nitrates. There is limited evidence to suggest that patients who fail on one of the inhibitors might respond on another. Finally, a recent study from the U.S. assessed 7 brands of herbal tablets/capsules that were marketed for ED and found significant concentrations of

**Table 2**
**Comparison of PDE-5 inhibitors**

| *PDE-5 inhibitor* | *Dose (mg)* | *n* | *GEQ (Active versus Placebo)* | *Adverse Events* | |
|---|---|---|---|---|---|
| Sildenafil *(21)* | 50–100 | 219 | 65% versus 11% | Headache | 18% |
| | | | | Flushing | 15% |
| | | | | Dyspepsia | 2% |
| Tadalafil *(23)* | 10–20 | 216 | 56–64% versus 25% | Headache | 8% |
| | | | | Flushing | 4% |
| | | | | Dyspepsia | 11% |
| Vardenafil *(24)* | 10–20 | 452 | 54–72% versus 13% | Headache | 12% |
| | | | | Flushing | 10% |
| | | | | Rhinitis | 8% |

GEQ = General Efficacy Question: "has the treatment you have been taking improved your erections"?

sildenafil or tadalafil in certain products. Given that the pharmaceutical products detected might have potentially fatal interactions with nitrates, it is clear that physicians should be alert to the potential contents of some of these over-the-counter products *(26)*.

#### Sublingual Medications

Sublingual apomorphine has been suggested as a potential therapy for ED in diabetes. However, the 22% response to the global efficacy question regarding erections on those taking active apomorphine SL was not significantly different from the 17% response on placebo, suggesting that apomorphine SL has a limited use for diabetic men with ED *(27)*. Interestingly, a study of the potential of sublingual sildenafil to treat ED in diabetes suggested that the dose of 20 mg was effective and safe. Sublingual sildenafil is rapidly absorbed and is unaffected by food ingestion in comparison to oral sildenafil, and therefore has a faster onset of action with a lower dose. It may be in the future that sublingual sildenafil may be most cost effective and provide a more predictable onset of action *(28)*.

#### Other Pharmacological Therapies

1) Intraurethral delivery of a pellet of alprostadil by a slender applicator inserted into the urethra is commonly known as MUSE (medicated urethral system for erection). After the patient delivers the pellet into the urethra, it gradually dissolves allowing the prostaglandin to diffuse into the corpus cavernosum. Initial placebo controlled studies of men with ED of diverse etiologies showed a 65% response rate *(29)*. However, penile pain seems to occur in more than 10% of application and a more recent report suggested that most men found intracavernosal alprostadil more acceptable and indeed more efficacious than MUSE *(30)*; the long-term usage of MUSE has also been disappointing *(31)*.
2) Self-injection therapy: Before the advent of the PDE-5 inhibitors, intracavernosal self-injection was a common method of treatment of ED in men with diabetes. This was initially described using the vasoactive agent papaverine *(32)*, but was later superseded by the prostaglandin E1 alprostadil. By 1990, Alexander showed that it was quite feasible for a diabetes physician to offer a treatment service for ED within a diabetes clinic teaching the techniques of self-injection *(33)*. With repeated use, care should be taken to avoid infections and fibrosis: the major side effect appears to be pain at the site of injection. Unwanted side effects of self-injection therapy include the risk of priapism (sustained unwanted erection) and prolonged use, particularly of papaverine, may lead to fibrosis *(34)*.

### *Vacuum Devices*

When medical treatment fails, vacuum tumescence (erection) devices tend to work irrespective of the cause of the ED. Such devices have been available for over 30 years and they induce erection by a negative pressure, drawing blood into the penis and retaining it. After the erection is achieved a constriction band is applied to the base of the penis that prevents the blood from leaving. The apparatus itself consists of a plastic cylinder to which the pump is attached. Trials of such therapy in diabetic men have shown results comparable with nondiabetic men suggesting that it is an effective treatment even in patients who might have extensive complications, including vascular disease and autonomic dysfunction *(35–37)*. Thus these devices seem to be a safe and efficacious treatment for ED in diabetes and are relatively inexpensive. Minor side effects might include discomfort or pain from the constriction band; some complain (especially the female partner) that the penis feels cold and there might be discomfort with ejaculation. Although the use of vacuum devices has declined since the advent of the PDE-5 inhibitors, they certainly have a place for patients who may not respond to or cannot use oral therapy.

## CONCLUSIONS

The development of the PDE-5 inhibitors at the end of the 20th century has revolutionized the management of ED by decreasing reliance on more invasive options. Multiple trials of sildenafil, tadalafil, and tardenafil give level 1A evidence for efficacy although there are no studies directly comparing the efficacy of these three agents (Table 3). Most patients will wish to try another PDE-5 inhibitor, should the first choice fail, before considering more invasive options.

For those men who do not respond to oral PDE-5 inhibitors alone, there is some logic in combining agents *(17,38)*, although direct evidence from randomized controlled trials is still lacking (level 1C evidence). Alternatives include vacuum-constriction devices and intracavernosal injection of vaso-active drugs (both level 1C evidence).

**Table 3**
**Levels of evidence for ED treatments**

| *Treatment* | *Grade of recommendation* |
|---|---|
| Mono-therapy with PDE-5 inhibitor | 1A |
| Combination therapy with two PDE-5 inhibitors | 1C |
| Intraurethral alprostodil | 1B |
| Vacuum-constriction device | 1C |
| Intracavernosal injection of vaso-active drugs(paperavine or alprostadil) | 1C |

Finally, although not discussed in this chapter, for those patients failing to respond to any pharmaco or physical therapies, referral to a urologist for the consideration of penile prosthesis might be considered *(38)*. Similarly, patients with local and structural penile abnormalities such as Peyronie's disease warrant referral to a urologist.

Although extremely rare in patients with ED and diabetes, hypogonadism may be best managed by and endocrinologist.

For the future, preliminary data suggest that tetrahydrobiopterin (which increases NO production and improves endothelial function) might be useful in the management of ED *(39)*. In the meantime, use of combination therapies in those who are nonresponsive to PDE-5 inhibitors alone appears sensible and may result in improved erections *(17,38)*.

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# 25 Sexual Dysfunction in Women with Type 2 Diabetes

*Ann J. Brown and Kathryn P. Lowry*

***CONTENTS***



**Summary**

Many women with type 2 diabetes report symptoms of female sexual dysfunction (FSD). Although sexual dysfunction is a well-established complication of type 2 diabetes in men, it has not been well-studied in women with diabetes. Information on the prevalence and etiology of FSD in diabetes is increasing but still sparse. Because few studies have examined FSD in type 2 diabetes exclusively, in this chapter we review available literature in both type 1 and type 2 diabetes.

Currently there are no guidelines for the evaluation and treatment of FSD specifically for women with type 2 diabetes. Various therapies have been examined in other populations, including phosphodiesterase inhibitors, estrogen therapy, and androgen therapy. Because the prevalence of FSD appears to be high, providers should address sexual function in diabetes management and be familiar with diagnostic and therapeutic options.

**Key Words:** Female sexual dysfunction; diabetes mellitus; libido; hypoactive sexual desire disorder.

## PREVALENCE OF FEMALE SEXUAL DYSFUNCTION IN TYPE 2 DIABETES

The American Foundation of Urologic Disease classifies female sexual dysfunction into four categories: hypoactive sexual desire, sexual arousal disorder, orgasmic disorder, and sexual pain disorders *(1)*. Hypoactive sexual desire is the persistent or recurring deficiency (or absence) of sexual fantasies/thoughts and/or receptivity to sexual activity, which causes personal distress. Sexual arousal disorder is the persistent or recurrent inability to achieve or maintain sufficient sexual excitement, expressed as a lack of excitement or a lack of genital or other somatic responses. Orgasmic disorder is the persistent or recurrent difficulty, delay, or absence of attaining orgasm after sufficient sexual stimulation and arousal. Sexual pain disorder includes dyspareunia (genital pain associated with sexual intercourse); vaginismus (involuntary spasm of the vaginal musculature that causes interference with vaginal penetration), and noncoital sexual pain disorder (genital pain induced by noncoital sexual stimulation).

Women with type 2 diabetes appear to be at an increased risk of impairment in each of these categories. In one study, women with type 2 diabetes were significantly more likely than age-matched controls to report lack of libido (77% versus 20%), diminished clitoral sensation (62.5% versus 20%), vaginal dryness (37.5% versus 20%), vaginal discomfort (41.6% versus 20%), and orgasmic dysfunction (49% versus 0%) *(2)*. Similarly, another study found that women with type 2 diabetes reported significantly lower levels of sexual desire, sexual satisfaction, and interest in sexual activity than age-matched controls. Additionally, more diabetic women reported inadequate lubrication and dyspareunia *(3)*.

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## CORRELATIONS OF FEMALE SEXUAL DYSFUNCTION IN WOMEN WITH DIABETES

Generally, male sexual dysfunction in diabetes is attributed to neurogenic or vascular complications of diabetes, specifically diabetic neuropathy. However, there is little evidence available for this relationship in women *(4)*. Although it is true that women with diabetes are at risk of diminished or altered sensation, this impairment does not necessarily correlate with female sexual dysfunction. For example, Erol and colleagues *(5)* found that both women with type 1 and type 2 diabetes demonstrated somatic sensory attenuation at genital and extragenital sites compared to controls. Furthermore, over half (55%) of the diabetic women met criteria for sexual dysfunction, whereas no women in the control group had impaired sexual function. However, there was no association between diminished sensation and subjective reports of sexual dysfunction.

In contrast to male sexual dysfunction, female sexual dysfunction in diabetes is thought to be more strongly associated with psychosocial factors than somatic factors *(6)*. Depression in particular appears to be an important correlate of FSD in diabetes. After controlling for age, body weight, and the presence of cardiovascular disease in a large, population-based study, approx 20% of women with type 2 diabetes met criteria for depression *(7)*. In a study of men and women with type 1 diabetes *(8)*, four times as many women with sexual dysfunction met criteria for clinical depression as women without sexual dysfunction, whereas there was no difference in the rate of depression between men with and without sexual dysfunction. Depression in women was significantly associated with decrease in libido, decreased arousal, and general sexual dysfunction whereas none of these relationships existed in men. Moreover, although duration of diabetes and the presence of diabetic complications were significant predictors of sexual dysfunction in men, they were not predictors in women.

Women with type 2 diabetes are also more likely to report dissatisfaction with their sexual relationships *(2,3)*. Schreiner-Engel and colleagues *(3)* have suggested that this dissatisfaction may be owing to the psychosocial challenges of adjusting to a chronic illness in late adulthood. For example, the development of diabetes may create relationship strain as both the woman and her partner are forced to adapt to this chronic condition long after relationship patterns have been established. The diagnosis of type 2 diabetes may also challenge her self-image and prompt concerns about sexual attractiveness *(3)*.

Collectively, these studies suggest that sexual dysfunction is a problem for both women and men with diabetes. Furthermore, sexual dysfunction in women does not appear to be related to physiologic complications of diabetes, but may instead be related to psychosocial factors. However, it is important to note that neither the physiological nor the psychological correlates of female sexual dysfunction in type 2 diabetes have been well-studied. Other, as yet unquantified, variables may play a role in FSD: for instance, although glycemic control was not associated with FSD in a study of patients with type 1 diabetes *(8)*, this relationship has not been examined in type 2 diabetes. Additionally, studies to date have provided only correlational data, and therefore conclusions about causality cannot be drawn. One potential confounder in the observed association between depression and sexual dysfunction *(8)* is the effect of certain anti-depressants, such as selective serotonin reuptake inhibitors (SSRIs), which can diminish sexual desire and orgasmic function in women *(9)*. This effect may partially explain the high rate of depression in diabetic women with sexual dysfunction and should be considered in future studies. More research is needed to identify other possible causal and confounding factors, as well.

Currently, no guidelines exist for the evaluation and treatment of sexual dysfunction specifically for women with type 2 diabetes. However, it is clear that sexual dysfunction is a common problem for these women and should be considered part of comprehensive management. The following recommendations for evaluation and treatment are based on guidelines for addressing female sexual dysfunction in the general population *(10,11)*.

## EVALUATION OF FEMALE SEXUAL DYSFUNCTION

Survey data suggest that female sexual dysfunction is often overlooked in the clinical setting, as the documented prevalence in the general population is much higher than the number of cases that are diagnosed *(12,13)*. This discrepancy could partly be owing to patients' reluctance to initiate a discussion about sexual dysfunction with their physician *(14)*. In one study, the number of patient reports of sexual dysfunction increased by sixfold when physicians queried patients about their sexual function *(15)*. Thus, provider inquiry is important for identifying potential cases of impaired sexual function.

**Table 1**
**Grades of recommendation for treatment options**

| *Treatment* | *Grade of recommendation* |
|---|---|
| Psychological counseling | 2C |
| Phosphodiesterase inhibitors | 2C |
| Estrogen therapy | 2C |
| Androgen therapy | 2C |

A comprehensive patient history to obtain medical, gynecologic, and psychosocial information may elicit possible causes of sexual dysfunction *(11)*. A detailed sexual history should include a history of sexual abuse or trauma, domestic violence, sexual preference, fear of pregnancy, and history or fear of contracting sexually transmitted diseases. A psychologist who specializes in sex therapy may be helpful in investigating some of these issues in detail.

Additionally, it is important to characterize the nature of the sexual dysfunction, including details about the onset and duration of the problems and ascertainment of the types of dysfunction present. The female sexual function index (FSFI) *(16)* is an example of one instrument that may be helpful in the assessment of type and severity of the dysfunction. The instrument and its scoring algorithm are available for public use and can be accessed at www.fsfiquestionnaire.com.

A complete physical examination should be performed, including a pelvic and comprehensive gynecologic exam. Women with vaginismus and/or dyspareunia may be unable to tolerate a bimanual exam. Cultures and vaginal samples should be obtained if vaginitis, cervical cancer, or sexually transmitted disease is suspected.

## TREATMENT OF FEMALE SEXUAL DYSFUNCTION

If the patient history and physical exam suggest any potential etiologies for sexual dysfunction, these causes should first be addressed. For example, it may be beneficial to change a medication regimen, treat a confounding medical condition more aggressively, or recommend individual or relationship counseling. If no etiology is readily identifiable, or if the patient has a history of abuse or trauma, the patient should be offered referral to a psychologist who can address these issues and their relationship to sexual dysfunction.

The use of medications to treat female sexual dysfunction is still in the investigational stage, and no studies have looked specifically at women with diabetes. The possible benefits of vasoactive agents, such as phosphodiesterase inhibitors, on female sexual response are being investigated but so far have not yielded convincing evidence *(17)*. A few studies have suggested that estrogen therapy may increase sexual desire and improve vaginal dryness and vaginal atrophy in postmenopausal women, but there is not enough evidence available to recommend specific treatment regimens *(18)*. Recently, there has been an increased interest in the use of androgen therapy in women with sexual dysfunction owing to evidence that suggests that testosterone may improve sexual function in naturally and surgically menopausal women *(19)*. However, no modes of androgen therapy are currently approved for treatment of sexual dysfunction in women owing to insufficient data concerning the indications for use of androgen therapy and its long-term safety *(19)*.

At this time, none of these treatment options have been evaluated in women with type 2 diabetes who report sexual dysfunction. Because the etiology of female sexual dysfunction in diabetes is unknown, many of these treatments may not be effective or appropriate in these women. Research is needed to identify and evaluate treatment regimens for sexual dysfunction specifically for women with type 2 diabetes. Until these data are available, these forms of therapy are only weakly recommended (see Table 1).

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# 26 Depression in Type 2 Diabetes

*Miranda A. L. van Tilburg, Anastasia Georgiades, and Richard S. Surwit*

***CONTENTS***



**Summary**

Diabetes patients have a twofold increased risk of suffering from depression as compared to individuals without diabetes. This commonly overlooked comorbidity affects about a quarter of the diabetic population. Because depression among diabetes patients has been associated with decreased metabolic control, poor adherence to medication and diet regimens, a reduction in quality of life, it is of importance for health care providers to recognize and properly treat depression among diabetes patients. When screening for depression, it is important to take into account that the physical symptoms of depression and diabetes overlap to some degree. Also, when deciding on a treatment plan for depression in diabetic patients, the health care provider must be aware of the unique side effects of antidepressants in this population. Psychotherapy and pharmacotherapy are effective in treating depression in the presence of diabetes; both cognitive behavior therapy and selective serotonin reuptake inhibitors have been associated with glycemic improvement in some studies.

**Key Words:** Depression; glycemic control; depression treatment strategies.

## INTRODUCTION

Diabetes Mellitus is a significant risk factor for major depression. Both type 1 and type 2 diabetes patients have a twofold increased risk of suffering from depression as compared to individuals without diabetes. According to recent prevalence studies, approx 20–25% of patients with diabetes have symptoms of clinically relevant depression, and this number increases when a history of depression is taken into account *(1)*. Patients with diabetes have an increased risk for depression, similar to that seen in other chronic illnesses *(2–4)*. However, in diabetic patients the effects of depression may not be restricted to psychological and social consequences. Depression may be associated with impaired blood glucose control. A link between depression and glucose metabolism has been suggested for two reasons. First, depression is associated with dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, leading to increases in counterregulatory hormones, such as cortisol, which are known to play a role in metabolic control. Second, diabetes management largely depends on the behavior of the patient. Changes in diet and exercise, medication adherence, and blood glucose testing often significantly tax the coping system of a patient. Withdrawal behaviors and self-medication with food are common in depression, and can have serious consequences for self-management in patients with diabetes.

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## IDENTIFYING DEPRESSION IN DIABETIC PATIENTS

Despite the increased prevalence of depression among diabetes patients, only in a minority of cases is depression recognized and/or treated *(5,6)*. Diabetic patients should therefore be screened for depression at initial diagnosis, with changes in medical status, such as the development of complications, and with changes in treatment, such as the initiation of insulin therapy. Furthermore, it is important to recognize that depression is often recurrent. Relapses are common, and patients with a history of clinical depression should be closely monitored. In a study of patients with diabetes with a previous history of depression, the rate of relapse within a year was 82.6%, yet none of the patients was treated for depression prophylactically, i.e., maintained on antidepressants *(7)*.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the following core criteria for major depression must be met during the same two week period: depressed or sad mood for most of the day, nearly every day, and/or markedly diminished interest or pleasure in all or almost all activities most of the day, nearly every day *(8)*. For diagnosis, a total of five or more symptoms must be present, including: significant increase or decrease in weight or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, poor concentration or indecisiveness, and recurrent thoughts of death or suicide.

Identifying depression in diabetic patients may be challenging, because the physical symptoms of depression (such as fatigue, changes in weight, or sexual dysfunction) overlap with symptoms caused by diabetes or diabetic medications. Depending on the attribution made regarding the origin of the symptoms, depression could be under- or overestimated in individuals with diabetes. Several self-report questionnaires are available for screening purposes and for evaluating changes in mood owing to therapy. Lustman and Clouse *(9)* discuss five commonly used instruments that have been validated in diabetic populations: Beck Depression Inventory (BDI) *(10)*, Patient Health Questionnaire *(11)*, Depressive Cognitions Scale *(12)*, Zung Scale *(13)*, and the Center for Epidemiological Studies Depression questionnaire *(14)*. Of these, the BDI has been most extensively used in both research and clinical practice. It is easy to administer and score, but, as the scale incorporates many somatic symptoms (6 of 21 items), it is highly recommended that the higher cut-off of 16 for possible clinical depression be used in patients with diabetes *(10)*. Once clinical depression is suspected, based on self-report questionnaires, the diagnosis should be confirmed by a patient interview. A clinical interview is necessary because of possible inaccuracies in self-ratings, and to assess other possible explanations for depressive symptoms, such as medication use or illness. There are several standardized interviews that can be used by a trained clinician. The Structured Clinical Interview (SCID) *(15)* is considered the gold standard, but other interviews, such as the NIMH Diagnostic Interview Schedule *(16)*, or the Composite International Diagnostic Interview, have also been used successfully *(17)*.

## HOW CAN DEPRESSION EFFECT DIABETES CONTROL?

### *Counterregulatory Hormones*

In recent years, much has been learned about the biological changes associated with depression. These changes are so pronounced that some have suggested that depressive states can precipitate diabetes in susceptible individuals. Dysregulation of the HPA axis has been reported in both depression and diabetes, resulting in an increase in circulating levels of a number of counterregulatory hormones, such as cortisol. Compared to healthy controls, patients with very severe major depression may have elevated levels of plasma cortisol *(18,19)*, disruptions in the circadian pattern of cortisol secretion *(18–20)*, and abnormal responses to administration of dexamethasone, showing an early "escape" or nonsuppression of cortisol following a dexamethasone suppression test (DST) *(21–24)*. After clinical recovery from depression, cortisol indices return to normal *(25,26)*.

Along with cortisol abnormalities, depressed patients also show increases in other counterregulatory hormones. Plasma catecholamines, specifically norepinephrine *(27,28)* and epinephrine *(28,29)*, have been found to be significantly elevated in depressed patients compared to healthy controls.

There is evidence that the increase in counterregulatory hormones associated with depression results in a state of relative insulin resistance. Nathan et al *(26)* demonstrated a positive relationship between insulin resistance and cortisol secretion in depressed patients. Furthermore, hypoglycemia following an insulin tolerance test, and glucose utilization, measured by either intravenous or oral glucose tolerance tests, are reduced during depression and increased following clinical recovery *(30,31)*.

The HPA axis is not only dysregulated in depression, but may play a role in diabetes as well. Older studies have reported that cortisol levels are higher in diabetic patients than in healthy controls *(32,33)* and that the presence of diabetic complications such as neuropathy and retinopathy is associated with increased levels of cortisol *(34)*, although in these studies the effect of stress or, indeed, depression is unclear. Furthermore, diabetic patients are more likely to show DST nonsuppression compared to matched controls (43% versus 7%) *(35)*. However, hypoglycemia itself is a stimulus for cortisol release and therefore no firm conclusions about the presence of HPA dysfunction in diabetes can be made unless the blood glucose control is specifically stabilized. In addition, abdominal obesity, which is common among patients with type 2 diabetes, has been shown to be associated with abnormal DST results *(36)*. However, even in a study that eliminated patients who were obese or who were hypoglycemic during the DST, HPA irregularities were still found in nearly half of the diabetic patients examined *(35)*.

The significance of the occurrence of similar abnormalities of the HPA axis in both depression and diabetes is unclear. There has been very little research examining changes in counterregulatory hormone activity during depression in patients with diabetes. In a case study of a depressed woman undergoing Electro-Convulsive therapy, remission of depression along with reduced insulin requirement was found, but no changes in cortisol were observed *(37)*. In another case study, a man with diabetes showed DST nonsuppression while depressed and a normal DST following recovery from depression, suggesting increased cortisol release during depression in his case *(38)*.

The possibility that HPA dysfunction can lead to depression has also been investigated. Although there is no direct evidence showing that HPA axis dysregulation results in mood disturbance, drugs that block glucocorticoid synthesis, when administered with a maintenance dose of cortisol, have an antidepressant effect in a substantial majority of patients with depression *(39)*. Therefore, it appears possible that HPA axis hyperfunction in patients with diabetes could increase the risk of depression in diabetes. However, there is evidence to suggest that depression is more likely to *precede* diabetes onset in those with type 2 diabetes whereas depression *follows* the onset of diabetes in those with type 1 diabetes *(40,41)*.

### *Diabetes Regimen Demands*

Diabetes requires patients to adopt a complex self-care plan, including increased exercise, compliance with a healthy diet, blood glucose monitoring, and adherence to a complicated medication regimen, requiring appropriate timing of medication administration and coordination with meals. The intensity and complexity of the self-care regimen varies widely among patients depending on the type and stage of disease, but even for those managed with diet and exercise alone, self-care is often a difficult task. Fatigue, passivity, withdrawal behaviors, and concentration difficulties, typical for depression, may affect metabolic control by causing deterioration in diabetes self-care behavior. Depression among diabetes patients has been shown to be associated with decreases in required behaviors such as physical activity, keeping a healthy diet and adhering to medications *(42)*. In addition, a subgroup of patients may self-medicate with high starch foods *(43)*. A number of studies have demonstrated that decreases in adherence to self-care behaviors are associated with altered blood glucose levels *(44,45)*. Therefore, if depression disrupts self-care, it would also be expected to have a negative impact upon glycemic control.

To date, only a few studies have assessed the relationship between depression and self-care behavior in diabetes. For example, among elderly patients with type 2 diabetes, those suffering from depression performed home blood glucose monitoring less often than those who were not depressed, although there were no significant differences among the groups in regularity of exercise or frequency of doctor visits *(46)*. A history of major depression has been linked to drop-out from weight-loss programs among diabetic patients *(47)*. Even depressive symptoms below the cut-off for clinical depression are negatively correlated with such self-care behaviors as physician visits, diet adherence, exercise, and adherence to doctor's instruction for home glucose testing *(48–50)*. In a study of type 1 diabetic patients, frequency of self-monitoring of blood glucose partly mediated the relationship between depressive symptoms and HbA1c *(51)*; similar results have been found in type 2 patients *(9)*. These data indicate that even subclinical depressive symptoms may impact aspects of self-care. Depression may not impact all aspects of self-care, and given the wide variety in diabetes self-care regimens, disruptions in self-care may have also very different effects on the blood glucose control of individual patients.

The depression/self-care link may be more important in patients with complex self-care regimens than in patients who are treated with diet and exercise alone, or a simple oral medication regimen. One recent study *(52)* showed an association of depression with HbA1c only in patients who take multiple insulin injections per day. It is possible that patients with more complex regimens have less endogenous insulin, and more intrinsically unstable glycemic control, making them more liable to glycemic dysregulation by factors that alter their ability to follow the treatment plan. Alternatively, the frustration of dealing with a highly complex medical regimen may be the problem.

In summary, although at this time data are limited the available evidence suggests that depression, even at a subclinical level, is associated with deterioration of important aspects of self-care. As a result, diabetes control can be adversely affected.

## Is there an Association between Depression and Glycemic Control?

A number of studies have focused on the general relationship between depression and poor glycemic control. However, the results of these investigations have been mixed. In a recent review of the literature, Lustman and Clouse *(9)* concluded that depression is associated with decreased glycemic control but that the relationship is weak at best and might not be observable in all types of patients.

When testing the association between depression and control of blood glucose, some studies have compared depressed versus nondepressed populations, whereas others have correlated depressive symptomatology with glycemic control. The former type of study has more frequently reported associations between depression and glycemic control than the latter. For example, Gross and colleagues *(53)* reported that 55.7% of severely depressed patients have a HbA1c value above or equal to 8, compared to only 31.9% in the nondepressed group. Similar results have been reported by others *(3,7,40,54)*, although negative findings have been reported as well *(46,55,56)*. Engum and colleagues *(57)* reported no associations between hyperglycemia and depression.

Studies assessing the relationship of depressive symptoms and glycemic control have also reported mixed results, but overall no clear association has been demonstrated. In particular, numerous studies have failed to show an association between depression scores and HbA1c *(47,50,52,55,56,58)*. Small but significant correlations between depressive symptoms and glycemic control were reported by Van der Does *(59)* ($r = 0.16$) and Eaton et al *(44)* ($r = 0.12$), suggesting that even though statistically significant, these relations might not be clinically relevant. These observations are reinforced by the results of a meta-analysis that included 24 studies, and found much smaller effect sizes for studies using self-report questionnaires (Effect Size $r = 0.015$) compared to studies using standardized interviews or diagnostic criteria (Effect Size $r = 0.028$,) *(60)*.

Only a few of these studies (e.g., Van Tilburg et al *(51)* and Surwit et al *(52)*) accounted for the potential confounding effect of psychopharmacological treatment on metabolic control by excluding patients who were taking antidepressants Other studies have not excluded these patients. For example, in a study of 16 clinically depressed patients who showed improvement in glycemic control, 13 patients were taking antidepressant medications *(7)*. Antidepressants may impact blood glucose independent of their effect on depression *(61)*. Because a large number of depressed patients can be expected to take antidepressant medications, the reported associations between depression and glycemic control may have been mediated by antidepressive medications. Later in this chapter the pharmacological effects of antidepressants will be discussed in more detail.

Another consideration in interpreting studies of depression and glycemic control is the difference that may occur between patients with type 1 and type 2 diabetes. Some investigators have demonstrated a relationship between depression and metabolic control only for patients with type 1 diabetes. Van Tilburg et al found no correlation in 34 type 2 patients between BDI scores and HbA1c ($r = 0.06$), whereas there was a good correlation in 30 type 1 patients ($r = 0.44$) *(51)*. These results have been confirmed in larger samples. In a study of 805 type 2 patients, no relationship between depression and HbA1c was found *(52)*, whereas, in another study, a significant relationship was noted between depression and HbA1c in 276 type 1 patients *(48)*. Although depression seems to be more clearly related to deterioration of glycemic control in patients with type 1 diabetes, the type of diabetes might not be the most important dividing aspect between patients who are and who are not at risk for a negative impact of mood on glycemia. As noted earlier, some patients with diabetes are severely insulin deficient, and thus intrinsically more unstable. Thus, the complexity of the insulin regimen may prove to be a marker for patients at risk for dysregulation of glucose control related to mood *(49)*.

### *Depression and Diabetes Complications*

Although most evidence suggests that depression does not directly affect glucose control in many patients with type 2 diabetes, depression may affect other outcomes. The relationship of diabetes complications, such as neuropathy, retinopathy, nephropathy, sexual dysfunction, and macrovascular complications with depression has been examined in several studies. In a recent meta-analysis, depression was found to be associated with retinopathy, nephropathy, neuropathy, sexual dysfunction as well as macrovascular complications such as coronary heart disease, atherosclerotic vascular disease and ischemic heart disease *(62)*.

In addition to specific complications, several studies have shown that depression predicts the number of complications *(58,63–65)*, although this finding is not uniformly reported *(66)*. Furthermore, depression can impact mortality rates among diabetic patients. The Fremantle Diabetes Study *(70)*, using data of 1,273 type 2 patients observed that depression was significantly associated with excess all-cause and cardiac mortality after adjustment for demographic and diabetes-related variables and cardiovascular risk factors. After controlling for microvascular and macrovascular complications, depression was not significantly associated with excess mortality. Egede et al *(67)* found that the coexistence of depression and diabetes was associated with a increase in mortality in a community sample of 10,025 individuals, beyond that related to the presence of diabetes or depression alone. Similar results have been reported in a sample of 4,154 HMO patients who were followed for 3 years *(68)*. Both minor and major depression was associated with an increase in mortality. After controlling for several mediators such as diabetic complications the effect of major depression on mortality was reduced but still significant.

It is not always clear whether depression plays a role in the development of complications, or if complications generally precede and thus cause depression. Although studies have documented that depression increases the risk of developing diabetes *(16,69)*, there are also studies supporting the hypothesis that depression may be related to the burden of having diabetes *(70,71)*. Complications can lead to significant disability and reduction of quality of life, thereby inducing depression. Studies have shown that depression in diabetic patients is positively associated with functional impairment *(58,72,73)*, disease threat *(73,74)*, and missed physician appointments *(75)*, lending further support to the hypothesis that depression may often be secondary to the challenges of living with diabetes complications.

## TREATING DEPRESSION IN DIABETES

### *Pharmacological Interventions*

Pharmacological treatment of depression is associated with a specific set of side effects, some of which may cause particular problems for patients with diabetes (see Table 1). Most problematic are the older classes of antidepressants: tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOs). Common side effects for both include anticholinergic effects such as dry mouth, blurry vision, constipation, impaired concentration, sedation, urinary retention, and sexual dysfunction *(76,77)*. Some of these effects mimic symptoms of hyperglycemia, or may enhance problems already encountered by diabetic patients. TCAs can also have more serious cardiovascular side effects, such as orthostatic hypotension, cardiac arrhythmia, and even cardiac arrest *(76)*. TCAs may disrupt glucose metabolism by increasing catecholamine function, leading to increased gluconeogenesis and blockage of insulin release *(78,79)*. TCAs are also associated with weight gain *(80)*. In addition, the use of MAOs can result in hypoglycemia *(81–83)* by converting hydrazine and nonhydrazine types to hydrazones. These agents produce hypoglycemia by blocking the acylcarnitine translocase enzyme responsible for long chain fatty acid oxidation, which serves as the energy source for glyconeogenesis,

Lustman and colleagues *(79)* conducted a placebo-controlled study of nortriptyline for depression in patients with both type 1 and type 2 diabetes. Although nortriptyline reduced depressive symptoms as compared to placebo, it did not result in a significant reduction of glycosylated hemoglobin. Because nortryptyline may actually increase glycosylated hemoglobin, the authors showed that, when the direct metabolic affects of the drug are accounted for, improvement in depression had an independent positive effect on metabolic control. Compliance with treatment medications and with home glucose monitoring was not improved in this study.

On the other hand, the use of selective serotonin reuptake inhibitors (SSRI), such as fluoxetine, in patients with diabetes has been associated with greater weight loss, decreased glycosylated hemoglobin, and decreased daily insulin dosage compared to placebo *(84–86)*. Studies show that SSRIs relieve depressive symptoms in diabetic

Table 1
Pharmacological Treatment Options for Depression in Diabetes Patients

| *Pharmacological Treatments for Depression in Diabetes Patients* | | |
|---|---|---|
| *Therapeutic approach* | *Grade of Recommendation* | *Clarity of Risk/Benefit* |
| **Selective serotonin reuptake inhibitors (SSRIs)**<br>Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertaline | Recommended (1A) | Effect on glucose metabolism: neutral or favorable effect; Effect on weight: neutral or weight-loss |
| **Serotonin-norepinephrine reuptake inhibitors (SNRI)**<br>Duloxetine | Recommended (1B) | Effect on glucose metabolism: neutral; Effect on weight: neutral or weight loss |
| **Tricyclic antidepressants (TCAs)**<br>Amitriptyline, Nortriptyline | Not recommended for diabetes patients (2A) | Effect on glucose metabolism: inconsistent results; Effect on weight: significant weight gain |
| **Monoamine oxidase inhibitors (MAO's)**<br>Moclobemide, Phenelzine, Tranylcypromine | Not recommended for diabetes patients (2C) | Effect on glucose metabolism: has been associated with severe hypoglycemic episodes; Effect on weight: significant weight gain |
| **Tetracyclic antidepressants**<br>Mirtazapine | Unclear | Effect on glucose metabolism: unclear; Effect on weight: some weight gain |
| **Others**<br>Bupropion | Recommended (1B) | Effect on glucose metabolism: neutral; Effect on weight: neutral |

patients without affecting metabolic control. Goodnick and colleagues *(87)* conducted a 10 week open study of an SSRI, sertraline, in 28 patients with type 2 diabetes who met criteria for major depression. Sertraline was effective in relieving depression in this group of patients, but there was no effect on glycosylated hemoglobin. In two randomized controlled studies of the SSRI, fluoxetine, depressive symptoms were reduced, but only a trend towards improved glycemic control was found *(88,89)*.

The potential of SSRIs to lower weight and improve glycemic control make these drugs well-suited for use in patients with diabetes, although close monitoring is necessary regarding the possible need to lower insulin or oral agent doses to prevent hypoglycemia. The most common side effects of SSRIs are nervousness, sleep disturbance, sexual dysfunction, headache, and nausea *(90,91)*. However, because of their more favorable side effect profile as compared to TCA's and MAO's, and their potential to improve glycemic control, SSRIs are likely to be the primary pharmacological treatment choice for depression in persons who have diabetes.

## *Psychological Interventions*

Nonpharmacological treatments for depression may be particularly valuable for diabetic patients, because they do not have side effects adversely affecting glycemic control. Psychological interventions, such as cognitive behavioral therapy (CBT), are recognized treatment options for depression in the general population, and have been shown to be as effective as pharmacotherapy even in the treatment of severe depression *(92,93)*. CBT is a form of psychotherapy in which the therapist helps the patient to identify and correct unhelpful thoughts, such as unrealistic expectations, unwanted automatic thoughts, and maladaptive assumptions. These are replaced by more realistic thoughts and helpful coping mechanisms.

Lustman and colleagues *(94)* studied the effects of CBT, on glucose control in patients with type 2 diabetes. Fifty-one patients were randomly assigned to either 10 weeks of individual CBT or a control condition. Depressive symptoms decreased more in the CBT group at the end of 10 weeks than in the control group. Although no immediate effect of treatment on HbA1c was noted, CBT-treated patients showed somewhat lower HbA1c values at 6 months compared to the control patients *(94)*. Van der Ven et al *(95)* studied the effects of six weeks of CBT

or blood glucose awareness training on measures of depression and glycemic control in a sample of 107 patients with type 1 diabetes. Although depressive symptoms decreased in both treated and control subjects, no associated changes in HbA1c were observed. In a recent study by Georgiades, et al., 90 diabetic patients with significant depressive symptoms received a 12-week CBT intervention *(96)*. Depressive symptoms decreased significantly in both type 1 and type 2 patients, but fasting glucose levels and HbA1c did not change over time in either group.

Although based on limited data, at this time, psychosocial interventions for treating depression in diabetes may be effective.

## CONCLUSION

Patients with diabetes have an increased risk for depression. Depression has shown to be associated with reduced metabolic control, although not all patients are at equal risk. There may be a particular risk for dysregulation of glucose with depression in type 1 patients and type 2 patients who have lost their ability to produce endogenous insulin. Depression is also associated with the occurrence of diabetic complications. Health care providers should therefore be aware of the need to carefully monitor mood in patients with new significant complications or multiple complications. When screening for depression, it is important to take into account that the physical symptoms of depression and diabetes overlap to some degree. Also, when deciding on a treatment plan for depression in diabetic patients, the health care provider must be aware of the unique side effects of antidepressants in this population. TCAs and MAOs are associated with more severe side effects than SSRIs, and may have negative pharmacological effects on glucose metabolism. In addition to pharmacological approaches, behavioral treatments such as CBT have shown to be as effective in treating depression as pharmacological approaches. Thus, behavioral treatments and SSRIs should be the first choice in treating depression among diabetic patients.

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# 27 Atypical Forms of Type 2 Diabetes

*Vinaya Simha and Abhimanyu Garg*

***CONTENTS***



**Summary**

Patients with "typical" type 2 diabetes are generally obese and display varying degrees of insulin resistance and insulin secretory defects. The onset of type 2 diabetes occurs mostly after the third decade of life, and these patients do not spontaneously develop ketosis or need insulin for survival. Many other patients present with "atypical" forms of type 2 diabetes; insulin resistance or insulin secretory defects occur owing to certain other specific etiologies. These include various genetic and acquired causes leading to adipose tissue disorders, β-cell dysfunction or impaired insulin action. Other endocrinopathies and drug therapy may also result in atypical diabetes. Lipodystrophies are characterized by selective loss of adipose tissue leading to excess fat accumulation in aberrant tissues such as the liver and muscle, which causes insulin resistance. Although the degree of fat loss and the resultant metabolic abnormalities varies among patients with the different types of lipodystrophies, diabetes in most lipodystrophic patients is characterized by marked insulin resistance and high insulin requirements. Maturity-onset Diabetes of the Young (MODY) is a group of heterogeneous forms of monogenic diabetes characterized by autosomal dominant inheritance, young age at onset and pancreatic β-cell dysfunction. Similarly, mutations or deletions in mitochondrial DNA also cause diabetes owing to β-cell dysfunction, which is maternally inherited, whereas insulin receptor mutations cause autosomal dominant or recessive syndromes of extreme insulin resistance such as type-A insulin resistance syndrome, Rabson-Mendenhall syndrome, and Leprechaunism. The clinical features and management of patients with these rare syndromes are distinct from those for patients with typical type 2 diabetes. Recognition of these patients is important, as it helps to tailor therapy based on the underlying pathophysiologic process. These syndromes have also greatly contributed to our understanding of glucose homeostasis and the pathogenesis of diabetes in general.

**Key Words:** Type 2 diabetes; lipodystrophy; MODY; mitochondrial diabetes; insulin resistance syndromes.

## INTRODUCTION

Patients with type 2 diabetes, who account for 90–95% of all patients with diabetes, commonly have metabolic defects resulting in insulin resistance as well as relative insulin deficiency. These patients do not need insulin treatment for survival, though many may require insulin in the later stages for optimal glucose control. Ketoacidosis seldom occurs spontaneously, and decline in β-cell function is not owing to autoimmune processes. The vast

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**Table 1**
**Etiologic classification of Atypical type 2 diabetes**

| |
|---|
| A. Diabetes associated with adipose tissue disorders |
| *Genetic* |
| Congenital Generalized Lipodystrophy, types 1 and 2 (*AGPAT2* and *BSCL2* mutations) |
| Familial Partial Lipodystrophy (*LMNA*, *PPARG* and *AKT2* mutations) |
| Mandibuloacral Dysplasia associated Lipodystrophy (*LMNA* and *ZMPSTE24* mutations) |
| *Acquired* |
| Highly Active Anti Retroviral Therapy-induced Lipodystrophy in HIV infected patients |
| Acquired Generalized Lipodystrophy |
| Acquired Partial Lipodystrophy |
| B. Diabetes owing to impaired $\beta$-cell function |
| *Genetic* |
| MODY1 (*HNF4A* mutations) |
| MODY2 (*GCK* mutations) |
| MODY3 (*TCF1/HNF-*$\alpha$ mutations) |
| MODY4 (*IPF-1* mutations) |
| MODY5 (*TCF2/HNF-1*$\beta$ mutations) |
| MODY6 (*NEUROD1* mutations) |
| Mitochondrial DNA mutations |
| *Acquired* |
| Disorders of exocrine pancreas owing to pancreatitis, trauma, surgery, cystic fibrosis, or hemochromatosis |
| C. Diabetes owing to impaired insulin action |
| *Genetic* |
| Type A Insulin Resistance (INSR mutation) |
| Rabson-Mendenhall syndrome (INSR mutations) |
| Leprechaunism (INSR mutations) |
| *Acquired* |
| Type B Insulin Resistance owing to anti-insulin receptor antibodies |
| D. Diabetes owing to other endocrinopathies |
| Acromegaly, Cushing's syndrome, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma |
| E. Diabetes owing to drug therapy |
| Glucocorticoids, Pentamidine, Nicotinic Acid, Diazoxide, Thiazides, β-adrenergic agonists, α-Interferon |

majority of patients with "typical" type 2 diabetes are obese, and their clinical features and management has been discussed in earlier chapters. In contrast, "atypical" forms of type 2 diabetes are not necessarily associated with the obesity phenotype, and are characterized by a variety of distinct clinical features. The etiology of these uncommon varieties of diabetes involves several genetic and acquired defects, based on which this diverse group of disorders can be classified, as shown in Table 1. Studying these rare forms of diabetes not only enhances our understanding of the pathophysiology of glucoregulation, but also helps us identify patients who may require unconventional therapeutic interventions. The clinical features, etio-pathogenesis and management of a few atypical forms of type 2 diabetes, which are distinct from the hitherto discussed typical variety, are reviewed in this chapter.

## DIABETES ASSOCIATED WITH ADIPOSE TISSUE DISORDERS: LIPODYSTROPHY SYNDROMES

Lipodystrophies are a heterogeneous group of inherited or acquired disorders, characterized by selective loss of adipose tissue. The pattern and extent of adipose tissue loss varies among the different types of lipodystrophies. Further, there is considerable genetic heterogeneity, with mutations in six genes, *AGPAT2*, *BSCL2*, *LMNA*, *PPARG*, *ZMPSTE24*, and *AKT2*, having been described in patients with various forms of lipodystrophy *(1–7)*. Based on the extent of fat loss (localized, partial or generalized), etiology (genetic or acquired), and other

**Table 2**
**Classification of lipodystrophies**

| |
|---|
| A. Inherited (Genetic) lipodystrophies |
| *Autosomal recessive* |
| Congenital Generalized Lipodystrophy, types 1 and 2 |
| Lipodystrophy associated with mandibuloacral dysplasia, types A and B |
| Lipodystrophy associated with SHORT syndrome |
| Lipodystrophy associated with neonatal progeroid syndrome |
| *Autosomal dominant* |
| Familial Partial Lipodystrophy |
| Lipodystrophy associated with SHORT syndrome |
| Lipodystrophy associated with Hutchinson-Gilford progeria syndrome |
| Pubertal-onset generalized lipodystrophy |
| B. Acquired lipodystrophies |
| HAART-induced lipodystrophy in HIV infected patients |
| Acquired Partial Lipodystrophy |
| Acquired Generalized Lipodystrophy |
| Localized lipodystrophy |

associated features, lipodystrophies can be classified as shown in Table 2. The prevalence of diabetes is not the same in all forms of lipodystrophy. In general, the severity of metabolic complications in lipodystrophic patients correlates with the severity of fat loss. Accordingly, diabetes is highly prevalent among patients with generalized lipodystrophies, both congenital and acquired. It is also seen quite commonly in patients with familial partial lipodystrophies, whereas patients with acquired partial lipodystrophy do not show an increased prevalence. Diabetes in lipodystrophic patients is characterized by marked insulin resistance, and they often have a high insulin requirement compared to other patients with type 2 diabetes. They also have many distinct clinical features, and great progress has been made in recent years in understanding the genetic basis of these disorders. A brief overview of the pathophysiology and clinical features of these syndromes are presented in this chapter, and interested readers are referred to more comprehensive reviews published recently *(8–10)*.

## *Genetic forms of Lipodystrophies*

### Congenital Generalized Lipodystrophy

Clinical features: Congenital generalized lipodystrophy (CGL) or Berardinelli-Seip syndrome is a rare autosomal recessive disorder with about 300 reported cases. Although described in patients of various ethnic origins, significant clusters of patients seem to be localized to some regions in Brazil and Lebanon. Affected patients have near complete absence of subcutaneous (sc) adipose tissue from birth leading to marked prominence of muscles and veins. During childhood, they are noted to have a voracious appetite, accelerated growth and advanced bone age. Umbilical hernia or prominence of the periumbilical skin, and an acromegaloid appearance owing to enlargement of hands, feet and mandible are other common features (Fig. 1A). Hepatomegaly from fatty infiltration may be seen at birth or later in life and may be accompanied by splenomegaly. Acanthosis nigricans is often observed over the neck, axilla, groin and trunk. Post pubertal girls develop clitoromegaly and features of polycystic ovarian syndrome. Less commonly, some patients develop multiple focal lytic lesions in the appendicular skeleton, hypertrophic cardiomyopathy and mild mental retardation *(11–14)*.

Genetics and molecular basis: Genome wide linkage analysis of several pedigrees and positional cloning strategies have led to the identification of two genetic loci for CGL: the 1-acylglycerol 3-phosphate-O-acyltransferase 2 (*AGPAT2*) gene on chromosome 9q34 *(1,15)*, which is associated with CGL1, and the Berardinelli Seip Congenital Lipodystrophy 2 (*BSCL2*) gene located on chromosome 11q13, which is associated with CGL2 *(2)*. However, certain patients with CGL do not have mutations in either *AGPAT2* or *BSCL2* and their pedigrees do not show linkage to these loci, thus suggesting the presence of additional CGL loci *(14)*.

AGPAT2 belongs to the superfamily of acyltransferase enzymes *(16)* and is involved in the biosynthesis of triglycerides and glycerophospholipids from glycerol-3-phosphate by esterifying the *sn-2* position of

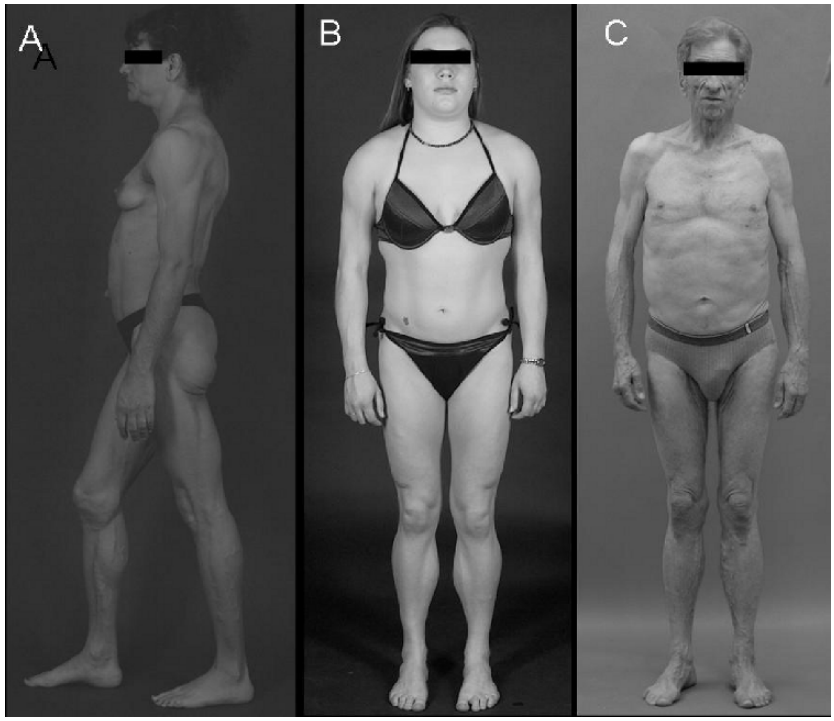


**Fig. 1.** Physical characteristics of patients with lipodystrophies. **A.** A 36-year-old Caucasian woman of Hispanic origin with congenital generalized lipodystrophy showing almost complete lack of sc fat with prominent veins and musculature. Acanthosis nigricans in the axilla and prominent umbilicus can also be seen. **B.** A 19-year-old Caucasian woman with familial partial lipodystrophy, Dunnigan variety. Subcutaneous fat over the extremities is diminished, leading to muscular prominence, whereas fat in the face and submental region is not only preserved but also slightly increased. **C.** A 71-year-old Caucasian man with HIV infection showing marked loss of fat from the face, trunk and extremities, which was noticed a year after starting protease-inhibitor inclusive antiretroviral therapy.

lysophosphatidic acid with a fatty acid to form phosphatidic acid *(17)*. Defective AGPAT2 function is likely to impair triglyceride and glycerophospholipid synthesis in adipocytes, which might cause lipodystrophy. The second locus, *BSCL2*, encodes a 398 amino acid protein, seipin, whose physiological function still remains undefined, and thus its precise role in fat loss is not clear. Interestingly, the highest expression of *BSCL2* is detected in brain and testis *(2)*, and it is only weakly expressed in adipose tissue *(18)*. This pattern suggests that the loss of fat in CGL2 might be mediated by a central mechanism involving the brain; however, a direct role of *BSCL2* in adipocyte development and differentiation may still be possible.

Subtle phenotypic differences exist between CGL1 and CGL2. Patients with CGL2 have increased prevalence of cardiomyopathy and mental retardation, whereas focal lytic lesions in the appendicular skeleton are mostly seen in CGL1 patients *(13,14)*. Differences in body fat distribution have also been noted between the two genotypes *(19)*. Patients with CGL1 have loss of metabolically active fat from sc, intermuscular and intra-abdominal regions, but retain mechanical adipose tissue located in the palms and soles, orbit, scalp, and periarticular regions. However, CGL2 patients have more severe fat loss involving both the mechanical and metabolically active fat depots.

Diabetes and metabolic complications: Patients with CGL develop diabetes and other significant metabolic abnormalities very early in life. Extreme insulin resistance is a striking feature of this syndrome. Most patients have high fasting and post prandial insulin levels, often from birth. Onset of diabetes is usually seen during pubertal years *(12,20)*, but occasionally, neonates may also develop hyperglycemia. Development of diabetes during the early years may be influenced by other concomitant factors such as malnutrition and recurrent infections. It has been suggested that patients with CGL2 have earlier onset of diabetes and more severe insulin resistance *(21)*. However, in our experience *(1,14)* and in other reported case series *(13)*, many CGL1 patients also develop diabetes during their teens. Severe hypertriglyceridemia leading to recurrent pancreatitis, low HDL cholesterol levels and chronic steatohepatitis are other associated features.

The exact cause for insulin resistance in CGL patients is not clear. Euglycemic clamp studies have demonstrated severe reduction in total glucose disposal owing to reduced nonoxidative glucose metabolism and reduced activity of muscle glycogen synthase *(22)*. No abnormalities in the insulin receptor or the binding of insulin to its receptor have been identified; thus, a post receptor defect has been suggested *(23)*. Whether reduction in intracellular levels of phosphotidyl inositol (PI), which is involved in downstream insulin signaling, or accumulation of abnormal species of PI is responsible for the post receptor insulin resistance remains unclear *(17)*. Owing to the diminished triglyceride storage capacity in these patients, dietary triglycerides are diverted to the liver and skeletal muscle, leading to accumulation of triglycerides there, which ultimately may inhibit glucose transport *(24)*. Reduction of intramyocellular and intrahepatic triglyceride concentrations have been shown to ameliorate insulin resistance *(25,26)*. These patients have very low levels of serum leptin and adiponectin *(27)*, and leptin-replacement therapy has been shown to be effective in controlling hyperglycemia, hypertriglyceridemia and hepatic steatosis *(28)*, suggesting that hypoleptinemia may be partly responsible for the metabolic abnormalities. Hypoleptinemia may contribute to the hyperphagia often seen in these patients, and may also have a role in regulating fat storage in nonadipose tissues. Whatever the cause, the marked insulin resistance ultimately leads to β cell exhaustion and overt diabetes. Severe islet amyloidosis has been described on autopsy of a 24-year-old female patient with CGL who had diabetes from 18 years of age *(29)*. Similar findings have been reported in other patients with CGL *(30,31)*, which indicate that islet amyloidosis may be one of the mechanisms for irreversible loss of β cell function.

### Familial Partial Lipodystrophy, Dunnigan Variety

Familial partial lipodystrophy, Dunnigan variety (FPLD) is an autosomal dominant disorder first described in 1974 by Dunnigan and colleagues *(32)*. The estimated prevalence is about 1 in 15 million, and over 300 patients, mostly of European descent, have since been reported, making this the most prevalent form of Familial Partial Lipodystrophy (FPL) *(8)*. FPL is also associated with mutations in the peroxisome proliferator-activated receptor-γ (*PPARG)* gene and v-AKT murine thymoma oncogene homolog 2 (*AKT2*) gene. Additional loci are also likely as some patients do not harbor mutations in these three genes.

**Clinical features.** Patients with FPLD have normal body fat distribution at birth and during childhood. Following puberty, gradual loss of sc fat is noted from the extremities leading to muscular limbs. Variable fat loss from the trunk, especially anteriorly is also seen, and excess fat deposition may occur over the unaffected areas leading to a round face, double chin, dorsocervical hump, and excess supraclavicular fat (Fig. 1B). Whole body magnetic resonance imaging (MRI) reveals preservation of intermuscular and bone marrow fat *(33)*. Intraabdominal and intrathoracic fat are also preserved, and may actually be increased. Women with FPLD are more easily diagnosed than men, owing to the unusual muscular appearance of the extremities. Acanthosis nigricans and features of polycystic ovarian syndrome are seen in one out of four affected women. Hepatic steatosis is also a common feature of this condition *(34,35)*. In some patients, cardiac conduction system disturbances resulting in atrial fibrillation and congestive heart failure have been noted *(36)*.

**Genetics and molecular basis.** The genetic locus for FPLD has been traced to the *LMNA* gene located on chromosome 1q21-22 *(5,37)*. The *LMNA* gene encodes lamins A and C, which belong to the intermediate filament family of proteins that are involved in the nuclear lamina, providing structural integrity to the nuclear envelope *(38,39)*. Mutant lamins A and C may disrupt normal interaction with chromatin and other nuclear lamina proteins, resulting in apoptosis and premature death of adipocytes. However, this mechanism does not explain selective loss of fat from certain regions of the body.

**Diabetes and metabolic complications.** Among FPLD patients, metabolic abnormalities such as diabetes and hyperlipidemia are more prevalent among women than men *(40–42)*. Diabetes was usually noted in at least half the reported female subjects, whereas in men, the prevalence was less than 20% *(40)*. The usual age of onset is about 30 years, and diabetes is typically ketosis resistant and marked by significant insulin resistance. Excess fat deposition in unaffected areas, such as the chin, and previous pregnancies appear to increase the risk for diabetes in affected women, whereas age, family history of type 2 diabetes, menopausal status or *LMNA* variants do not appear to predict predisposition to diabetes *(42)*. The mechanism of insulin resistance and β-cell

destruction is probably similar to CGL. Islet amyloidosis has been noted in a FPLD patient with diabetes, but not in a nondiabetic individual with FPLD and features of insulin resistance *(34)*.

### Familial Partial Lipodystrophy Owing to PPARG Mutations

FPL owing to heterozygous missense mutations in the *PPARG* gene encoding the nuclear receptor PPARγ, have been identified in ten patients with FPL *(3,43–46)*. No case of homozygous mutations in *PPARG* gene have been reported, consistent with the embryonic lethality of homozygous gene deletion in a murine model. All affected subjects had normal adipose tissue distribution at birth, and developed fat loss during adolescence or during middle age. Fat loss usually affected the distal extremities, buttocks and face, and spared the trunk, where some patients had excess fat deposition. The majority of patients had acanthosis nigricans and hypertension, whereas features of PCOS were seen in about half. Hyperinsulinemia, hypertriglyceridemia and diabetes has been reported in most of the affected subjects. Onset of diabetes is usually during the third or fourth decade.

*PPARG* is highly expressed in adipocytes and has a critical role in regulating adipocyte development and differentiation *(47)*. It is therefore possible that *PPARG* mutations cause lipodystrophy by affecting adipogenesis. The pathogenesis of diabetes involves insufficient fat depots to buffer dietary triglycerides, as in other lipodystrophies, but because fat loss is not as severe as in CGL or FPLD, it is likely that dysfunction of residual adipocytes may also play a role *(48)*.

### Familial Partial Lipodystrophy Owing to AKT2 Mutations

Recently, a heterozygous missense mutation in the *AKT2* gene was reported in a family in which affected subjects developed partial lipodystrophy of the extremities, insulin resistance, diabetes mellitus and hypertension *(7)*. All affected subjects had hyperinsulinemia and glucose clamp studies in the proband demonstrated extreme hepatic and peripheral insulin resistance. Three of the four affected individuals developed diabetes in the third decade. AKT2 is a serine/threonine kinase expressed in insulin sensitive tissues and is involved in post receptor insulin signaling. Data from homozygous *AKT2* gene deletion in mice suggests that AKT2 also regulates the expression of *PPARγ*. Abnormal AKT2 functioning may cause lipodystrophy by decreasing adipocyte differentiation via *PPARγ* regulation or by dysfunctional postreceptor insulin signaling, which could also lead to development of diabetes.

### Mandibuloacral Dysplasia (MAD) Associated Lipodystrophy

MAD is a rare autosomal recessive disorder with about 40 reported cases. The characteristic features of this syndrome include postnatal resorption of bone in the mandible, clavicles and terminal phalanges (acro-osteolysis) in addition to fat loss, suggesting a common genetic or metabolic defect affecting both the skeleton and adipose tissue *(49)*. In addition, these patients also have short stature, delayed closure of cranial sutures, joint contractures, mottled skin pigmentation, and features of premature ageing. Hyperinsulinemia and insulin resistance has been widely reported in MAD patients *(49–51)* whereas overt diabetes has been reported in 4 subjects. Two patterns of lipodystrophy have been described in patients with MAD *(49)*. Type A pattern is characterized by partial loss of sc fat from the extremities with normal or excess fat over the face and neck, whereas Type B pattern involves a more generalized loss of sc fat. *LMNA* mutations have been described in MAD patients with Type A lipodystrophy *(52)*, and compound, heterozygous mutations in *ZMPSTE24*, a gene encoding a zinc metalloproteinase that is essential for post translational modification of prelamin A *(6)* have been reported in some MAD patients with Type B lipodystrophy. The detrimental effects of *ZMPSTE24* mutations may be either owing to accumulation of prenylated prelamin A or owing to lack of mature lamin A. Some MAD patients have no mutations in either *LMNA* or *ZMPSTE24*, suggesting additional as yet unmapped loci.

## *Acquired Lipodystrophies*

### Lipodystrophy in HIV infected subjects (LDHIV)

LDHIV is a newly identified variety of acquired lipodystrophy, but by far the most prevalent form of any lipodystrophy. HIV-1 protease inhibitor (PI) therapy appears to be the major culprit, but some studies suggest that nucleoside reverse transcriptase inhibitors might contribute to it as well *(53–55)*. On average, 40–50% of

ambulatory HIV-infected patients in the United States demonstrated abnormalities in body fat distribution *(56)*, and more than 100,000 patients in the United States are estimated to be afflicted by this condition *(8)*. LDHIV may present with diverse morphological features, and it is a matter of debate whether LDHIV represents a composite of different syndromes. The majority of patients demonstrate loss of sc adipose tissue from peripheral regions including the face, extremities, and gluteal region (Fig. 1C), a phenomenon sometimes referred to as lipoatrophy *(57)*. In most of these patients, sc adipose tissue over the trunk and the visceral adipose tissue are reported to be either preserved or rather increased (lipohypertrophy). Prominence of the dorsocervical fat pad (buffalo hump) and breasts may also be seen. In most patients, features of fat loss and fat excess coexist.

Patients with LDHIV often have dyslipidemia, insulin resistance and hepatic steatosis. Dyslipidemia in the form of hypertriglyceridemia, hypercholesterolemia and low HDL-cholesterol is common, and may sometimes precede changes in body fat distribution. Although the prevalence of hyperglycemia (6–20%) in these patients is not as high as dyslipidemia (50–70%) *(58,59)*, it is a significant problem. Management of diabetes may be complicated by concomitant infections such as Hepatitis C, and use of drugs such as nucleoside reverse transcriptase inhibitors (which increase risk for lactic acidosis), megesterol acetate or growth hormone, which can worsen hyperglycemia and also limit the use of other anti diabetic agents such as metformin and thiazolidinediones (TZDs).

### Acquired Generalized Lipodystrophy (AGL)

AGL is another rare disorder and has been reported in approx 80 patients, with a marked female preponderance *(60)*. It is characterized by selective loss of adipose tissue from large regions of the body occurring after birth. Adipose tissue loss usually involves the face, trunk, and extremities, and sometimes also spreads to the palms and soles. Intraabdominal fat may also be lost whereas retro orbital and bone marrow fat are generally well preserved. The loss of adipose tissue may occur precipitously, within a few weeks, or may be more insidious over several months. In some patients, fat loss is preceded by the appearance of tender, inflamed sc nodules owing to panniculitis, but in others the disease is associated with autoimmune diseases such as juvenile dermatomyositis, Sjogren's syndrome, juvenile rheumatoid arthritis, chronic active hepatitis, and autoimmune hemolytic anemia. However, in over half the reported cases of AGL, neither panniculitis nor autoimmune diseases have been reported. Although autoimmune destruction of adipocytes may explain fat loss in the panniculitis and autoimmune variety, little is known about the pathogenesis of idiopathic variety of AGL.

Similar to CGL, patients with AGL also show marked insulin resistance, including hyperinsulinemia, diabetes, hypertriglyceridemia, and low serum HDL cholesterol levels. Diabetes usually presents a few years after the onset of lipodystrophy, but in some instances it appeared almost simultaneously or even preceded the onset of lipodystrophy. The pathogenesis of diabetes in AGL is probably similar to that in CGL. However, patients with the panniculitis variety of AGL have a lesser prevalence of diabetes than the other two varieties of AGL *(60)*, suggesting that some subtle differences may exist among the different forms of AGL, and between AGL and CGL. Severe hypertriglyceridemia may be associated with eruptive xanthomas and pancreatitis. Other abnormalities include nonalcoholic steatohepatitis, acanthosis nigricans, and menstrual irregularities. Low levels of serum adipokines such as leptin and adiponectin have also been reported *(27)*, and leptin replacement therapy appears to be a promising option to control the metabolic abnormalities *(28,61)*.

### Acquired Partial Lipodystrophy (APL)

Over 250 patients with APL, also known as Barraquer-Simmons syndrome, have been reported in the literature *(62)*. APL is characterized by the gradual onset of bilaterally symmetrical loss of sc fat from the face, neck, upper extremities, thorax, and abdomen in a cephalocaudal sequence, sparing the lower extremities. Often, excess fat accumulation is seen over the lower abdomen, gluteal region, thighs and calves. The onset of fat loss usually occurs during childhood or adolescence, at a median age of 7 years, whereas the excess fat accumulation is noted to occur at the onset of puberty or with weight gain. Women are reportedly affected four times more often than men *(62)*. Unlike other lipodystrophies, patients with APL rarely develop metabolic abnormalities related to insulin resistance. Diabetes has been reported in about 12–14% of affected individuals, which is only a little more than the prevalence of type 2 diabetes in the general population. However, this condition is often associated with membrano-proliferative glomerulonephritis and other autoimmune disorders, such as systemic lupus erythematosus, dermatomyositis/polymyositis, vasculitis, and undifferentiated connective tissue diseases.

## *Management of Diabetes in Patients with Lipodystrophy*

### Diet

Because inability to store dietary triglycerides in adipose tissue is the major defect in lipodystophy, low fat diets have generally been recommended. Such a diet should potentially be able to reduce the accumulation of fat in the liver, muscle and other nonadipose tissues, and thus ameliorate insulin resistance. However no controlled studies have been done to test this hypothesis. Lipodystrophic patients, especially those with generalized lipodystrophy and hypoleptinemia, have a voracious appetite, and, on a free diet, their daily energy consumption has been reported to range from 3,000 to 5,000 kcal *(12)*. Energy restriction has been shown to be beneficial in improving metabolic abnormalities in individual patients in the short term *(63–65)*. Appetite suppressant drugs such as fenfluramine have been used in some patients with CGL *(63,66)*, underlining the importance and difficulty of caloric restriction. Eucaloric substitution of medium chain triglycerides has been shown to improve insulin resistance in a patient with AGL *(67)*. In the absence of well controlled studies, it is prudent to recommend a diet that provides enough energy based on the patient's age and sex, with emphasis on the use of complex carbohydrates and *cis*-monounsaturated fats. Patients with extreme hypertriglyceridemia may benefit from extremely low fat diets.

### Oral Hypoglycemic Agents

Besides reducing the dietary triglyceride load, attempts to improve triglyceride storage capacity are likely to benefit lipodystrophic patients. TZDs, by activating PPARγ receptors, promote adipocyte differentiation and development, and thus may help to reduce hepatic steatosis and insulin resistance. Arioglu et al. *(68)*, in an open-label trial, administered troglitazone for 6 months to 16 patients with partial lipodystrophy and 3 with generalized lipodystrophy. The mean hemoglobin A1c (HbA1c) concentrations decreased by 2.8% in the 13 patients with diabetes. A significant decline in the fasting serum triglycerides and free fatty acids was also noted, and MRI revealed an increase in sc adipose tissue with no changes in visceral adipose tissue. Troglitazone, however, has been withdrawn from the market in view of its hepatotoxicity, and similar trials with the newer TZDs have not been reported. Rosiglitazone has been shown to have inconsistent benefits in individual patients with FPLD *(69,70)*. Scientifically, TZDs are appealing for FPL patients with *PPARG* mutations as they may directly overcome the genetic defect. However, the response to rosiglitazone treatment in these patients has been inconsistent *(45)*. In patients with LDHIV, open label and placebo controlled trials of TZDs in small groups of patients have shown beneficial effects on insulin resistance and body fat distribution, but no consistent effect on plasma glucose and lipids *(71–75)*. Hypertriglyceridemia has been noted with the use of rosiglitazone *(72,73)*, and these drugs should be used with caution as they have potential for other toxicities, including fluid retention and hepatotoxicity. Metformin has also been reported to improve insulin resistance and decrease visceral fat accumulation in patients with LDHIV *(74,76,77)*, but needs to be used cautiously in patients on nucleoside reverse transcriptase inhibitors as they may increase risk for lactic acidosis. However, no increase in lactate levels was noted with metformin therapy in these trials. Sulfonylureas can also be effectively used in patients with all types of lipodystrophies.

### Insulin

Insulin has generally been the mainstay of therapy for most patients with lipodystrophy and long standing diabetes. These patients often require large doses of insulin, and use of concentrated insulin solution U500 (500 units/mL) may help reduce the volume of injection. This would be especially useful in patients with generalized lipodystrophies who do not have sc fat and thus have difficulty with injections. Continuous sc insulin infusions have also been successfully employed in some patients, although it does not decrease their insulin requirement *(78)*.

### Novel Therapies

As mentioned previously, marked hypoleptinemia is seen in patients with lipodystrophy, especially those with generalized lipodystrophy and this may contribute to hyperphagia and other metabolic abnormalities. An open-label trial of leptin replacement therapy resulted in marked improvement in hyperglycemia and hyperlipidemia after 4 months of therapy *(28)*, and these benefits persisted after 12 months of treatment *(61)*. Leptin therapy has also been shown to improve insulin sensitivity and reduce intrahepatic and intramyocellular accumulation

of lipids *(25,26,79)*. Most of the patients studied had generalized lipodystrophy, but benefit has been observed in some patients with partial lipodystrophy as well *(61)*. A recent report of a placebo-controlled double-blind crossover trial of leptin treatment for 2 months in patients with LDHIV showed reduction in fasting serum insulin levels but no change in plasma glucose and lipids *(80)*. More controlled trials of longer duration are necessary to establish the utility of leptin therapy, but initial studies of leptin replacement therapy in hypoleptinemic patients have been promising. Anecdotal reports suggest that insulin-like growth factor-1 (IGF-1) may also be effective in lowering glucose and HbA1c levels in CGL patients *(81)*.

## DIABETES OWING TO GENETIC DISORDERS OF β-CELL FUNCTION

### *Maturity-Onset Diabetes of the Young (MODY)*

MODY is the term for a group of heterogeneous monogenic forms of diabetes, characterized by autosomal dominant inheritance, young age at onset (usually diagnosed before the age of 25 years), and pancreatic β-cell dysfunction. It has a worldwide distribution, and is estimated to account for 2–5% of patients with diabetes, although it may often go unrecognized. Depending upon the underlying genetic defect, patients display distinct metabolic and clinical features. The acronym was coined by Dr. Fajans and co-workers *(82)* following their original description of a group of nonobese children and teenagers with mild diabetes who differed from patients with classical type 1 "juvenile-onset" diabetes by having good metabolic control over a long term *(83)*. The monogenic nature of this disorder has been apparent only in the last decade or so following linkage and gene mapping studies *(84–89)*. Heterozygous mutations in six different genes have been identified in patients with MODY (Table 3), but close to a third of patients do not show mutations in any of the known genes, suggesting the

**Table 3**
**Genotypic and phenotypic characteristics of MODY**

| | *MODY 1* | *MODY 2* | *MODY 3* | *MODY 4* | *MODY 5* | *MODY 6* |
|---|---|---|---|---|---|---|
| Gene defect | *HNF-4α* | *GCK* | *HNF-1α (TCF1)* | *IPF-1* | *HNF-1β (TCF2)* | *NEURO-D1* |
| Gene locus | 20q | 7p | 12q | 13q | 17q | 2q32 |
| Protein function | Orphan nuclear receptor, Transcription factor | Glucose phospho-rylation enzyme | Transcription factor | Transcription factor | Transcription factor | Transcription factor |
| Primary defect | Insulin secretion | Glucose induced insulin secretion | Insulin secretion | Beta cell development | Insulin secretion | Beta cell development |
| Frequency (% of all MODY) | Rare | 8–63% | 21–64% | Rare | Rare | Rare |
| Diabetes onset | Adolescence, early adulthood | Early childhood | Adolescence, early adulthood | Adolescence, early adulthood | Early adulthood | Adulthood |
| Diabetes severity | Severe, progressive | Mild, minor change with age | Severe, progressive | Mild - moderate | Severe, progressive | Mild - moderate |
| Complications | Frequent, microvascular | Rare | Frequent, microvascular | Unknown | Frequent, microvascular | Unknown |
| Treatment | Sulphonyl urea, Insulin | Diet, exercise | Sulphonyl urea, Insulin | Insulin | Sulphonyl urea, Insulin | Insulin |
| Other features | Low serum triglycerides | Low birth weight | Renal glycosuria | | Renal and genital malforma-tions | |

presence of additional unidentified loci. Information about these rare disorders has enhanced our understanding of the regulation of insulin secretion and glucose homeostasis, and may provide clues to a better understanding of the genetic basis of type 1 and type 2 diabetes, as variants in many of the MODY genes have been associated with polygenic type 2 diabetes (90–92). Further, it is important to recognize patients with MODY, as those with different forms of MODY have different clinical courses and prognoses, and benefit from different therapeutic approaches.

The genetic and phenotypic characteristics of different MODY subtypes are summarized in Table 3, but, for clinical purposes, it would be useful to consider two broad categories of MODY: those with mutations in glucokinase (GCK) gene, and those with mutations in the various transcription factors. MODY patients with *GCK* mutations have milder, often asymptomatic diabetes, present since birth, which generally does not need pharmacologic intervention and is rarely associated with diabetic complications. On the other hand, MODY patients with transcription factor mutations usually manifest diabetes during adolescence, which is progressive and often requires insulin secretogogues or insulin therapy, and is associated with the typical chronic complications of diabetes.

### MODY Owing to *GCK* Mutations

MODY 2, owing to *GCK* mutations, is a common form of MODY, and has been reported in up to 60% of patients with MODY in France, where universal glucose testing is in vogue. A lesser prevalence of 15–20% is reported from other areas, and it has been described in persons of all racial and ethnic groups *(93)*.

**Pathophysiology.** More than 130 different mutations in GCK have been reported to cause MODY 2 *(86,94)*. Mutations in GCK lead to decreased activity of the enzyme and thus decreased glycolytic activity in the β cells. Insulin secretion by the β cells in response to glucose is dependent in large part on the ability of β cells to take up and metabolize glucose. Phosphorylation of glucose to glucose-6-phosphate is the rate limiting step in this process, and thus decreased activity of GCK, the enzyme catalyzing this critical step, leads to decreased glucose uptake and utilization causing a glucose sensing defect. Thus there is an increase in the blood glucose threshold that triggers insulin secretion from a normal basal concentration of about 90 mg/dL to approx 108–126 mg/dL. The dose response curve of glucose-induced insulin secretion is shifted to the right *(94)*, and patients have mildly increased basal and postprandial plasma glucose concentration. Because the defect lies in glucose sensing, and insulin synthesis is intact, the rise in plasma glucose with oral glucose challenge (usually < 50 mg/dL) is small, and closer to that seen in normal individuals than in patients with other forms of diabetes *(95,96)*. Hyperglycemia also results from defect in postprandial glycogen synthesis in the liver *(97)*. Homozygous *GCK* mutations cause complete deficiency of the enzyme, and are associated with low birth weight and permanent neonatal diabetes requiring insulin therapy *(98)*.

**Clinical features.** The clinical phenotype of MODY 2 is remarkably constant. Patients have mild fasting hyperglycemia throughout life (90–145 mg/dL), which may be apparent from birth. Approx 60% of the patients have fasting plasma glucose values less than 126 mg/dL *(95)*. Patients are rarely symptomatic and glycemic levels fall more often in the impaired fasting glucose or impaired glucose tolerance range. There is mild deterioration of fasting blood glucose with age, but even in patients in their eighth decade, fasting blood glucose rarely exceeds 180 mg/dL. Diabetes related complications are rare, and HbA1c is often in the upper normal range.

An interesting observation in patients with MODY 2 is the low birth weight, probably owing to the effect of low insulin levels on fetal growth *(99)*. However, if a mother with MODY 2 carries a fetus with a normal *GCK* gene, the child will be macrosomic if glucose control during pregnancy is not adequate.

**Treatment.** Pharmacological treatment is usually not necessary and most cases are successfully controlled with diet alone. A small number of patients may need additional therapy probably because they carry other susceptibility alleles to diabetes. Insulin therapy is necessary in about 2% of patients *(100)*. Intensive follow up is probably not necessary, and yearly review with HbA1c is considered appropriate *(93)*. These patients also have a low frequency of coronary heart disease as the classical risk factors for macrovascular disease such as hypertension, obesity and dyslipidemia are rare.

### MODY Owing to Mutations in Transcription Factors

Mutations in the transcription factors controlling various metabolic processes in the β cells and pancreatic development lead to the other known subtypes of MODY. Of these, MODY 3, owing to mutations in hepatocyte nuclear factor-1α (HNF-1α) or transcription factor 1 (TCF1) is the commonest form in most populations. More than 120 different mutations in this gene have been identified in persons of all racial and ethnic backgrounds *(94)*. MODY 1, owing to mutations in HNF 4-α, is relatively uncommon but has similar clinical and pathophysiological characteristics to MODY 3, because HNF-4α regulates the expression of HNF-1α. HNF-4α deficiency also affects triglyceride and apolipoprotein synthesis in the liver leading to reduction in serum concentrations of triglyceride, apolipoproteins CIII and AII, and lipoprotein (a) *(101)*. Mutations in HNF-1β cause MODY 5, which is also very uncommon. These patients may also manifest renal anomalies such as hypoplastic glomerulocystic kidney disease *(102)*, and genital abnormalities such as vaginal aplasia and rudimentary uterus *(103)*, as HNF-1β is widely expressed in these tissues. Similarly, MODY 4 and MODY 6, owing to mutations in insulin promoter factor-1 (*IPF-1*) and neurogenic differentiation factor 1 (*NEURO D1*), respectively, are also extremely rare. These transcription factors are critical for the embryonic development of pancreatic islets and exocrine pancreas, and homozygous mutations in *IPF-1* cause pancreatic agenesis *(104)*. The pathophysiology and clinical features of MODY 3, which is the commonest form of MODY, is discussed in the following section.

**Pathophysiology.** The exact β cell defect owing to HNF-1α mutations is not known, but probably involves alteration in the metabolic signaling pathways, which control insulin secretion *(105)*. Unlike MODY 2, "glucose-sensing" is intact, but insulin secretion in response to both glucose and arginine is deficient *(106)*. Like patients with MODY 2, patients with MODY 3 may also have only modest elevation in fasting plasma glucose levels, but, following oral glucose challenge, insulin secretion does not increase appropriately, leading to markedly elevated plasma glucose levels. Both the first and second phase of insulin secretion is affected, and there is progressive loss of insulin secretion capacity. These patients also exhibit renal glycosuria owing to the effect of HNF-1α mutations on renal glucose reabsorption.

**Clinical features.** Patients with HNF-1α mutations have normal fasting blood glucose and glucose tolerance under the age of 10 years, and show mild fasting hyperglycemia with subsequent development of diabetes during adolescence or early adulthood. The mean age of diagnosis of diabetes is 23 years, but it can vary over a wide range *(93)*. Disease penetrance is variable but increases progressively with age from 63% at age 25 years to 95% at age 55 years *(107)*. Hyperglycemia is often symptomatic and progressive. Osmotic symptoms may also result from renal glycosuria. Insulin resistance, obesity, and dyslipidemia are infrequently seen in these patients, but they are usually at high risk for microvascular complications *(100,108)*. Retinopathy and nephropathy are as common in MODY 3 patients as in patients with type 1 and type 2 diabetes matched according to the duration of diabetes and the degree of glycemic control.

**Treatment.** Treatment of MODY 3 patients is similar to treatment of other diabetic patients with prominent insulin secretory failure. Sulfonylureas or insulin can be used depending on glucose control. 30–40% of patients are reported to require insulin therapy *(94)*, but a recent randomized trial demonstrated increased sulphonylurea sensitivity in MODY 3 patients compared to type 2 diabetics with similar BMI and glycemic control *(109)*. This was ascribed to a preserved insulin secretory response to sulfonylureas and increased sensitivity to the insulin secreted. Further, Shepherd et al *(110)* have shown no deterioration in glycemic control when MODY 3 patients on long term insulin therapy were switched to sulfonylureas. More studies are needed to establish whether sulfonylureas are the optimal therapeutic approach in all patients with MODY 3.

## *Diabetes Owing to Mitochondrial DNA Mutations*

Mitochondrial DNA mutations leading to diabetes were first described in 1992 in a large pedigree with "maternally inherited diabetes and deafness" (MIDD) *(111)*, and was initially thought to result from defective oxidative metabolism in the skeletal muscle causing enhanced lactate flux to the liver and hyperglycemia via increased hepatic gluconeogenesis *(112)*. However, it is now well understood that mitochondrial diabetes results primarily from β-cell dysfunction. The most common mitochondrial mutation causing diabetes involves substitution of

guanosine for adenosine (A>G) at position 3243 of leucine tRNA (MT-LT1). About a dozen other point mutations in mitochondrial DNA are also associated with diabetes but are very rare *(113)*. The frequency of A3243G mutation among patients with type 2 diabetes is reported to range from 0.1–0.2% in the UKPDS cohort *(114)* to 1–2% among Japanese subjects *(115)*. Deletions in mitochondrial DNA are also associated with diabetes, mostly with a juvenile-onset, type 1-like diabetes *(116)*.

**Pathophysiology.** Hyperglycemic clamp studies in 2 individual patients with A3243G mutation and impaired glucose tolerance revealed decreased first and second phase insulin secretion with normal insulin sensitivity *(117)*. The cause for the insulin secretory defect in these patients is not entirely clear but is most likely a result of decreased ATP generation in the β cell, which alters glucose signaling similar to patients with *GCK* mutations. However, unlike MODY 2 patients, insulin secretory failure in patients with mitochondrial DNA mutations is progressive, and additional pathogenetic mechanisms such as impaired protein synthesis and accelerated ageing of the β cells may also play a role *(118)*.

**Clinical features.** Diabetes associated with MT-LT1 A3243G mutation is usually diagnosed in the 3rd to 5th decade, but may present as early as 10 years or as late as in the 6th or 7th decade *(119)*. Patients have normal or low BMI. Hyperglycemia is often mild and controlled by diet at diagnosis, but it tends to be progressive. Some patients become rapidly dependent on insulin therapy and may be diagnosed as type 1 diabetes. Most others resemble type 2 diabetes, and can be managed by diet and sulfonylureas for a few years before ultimately requiring insulin therapy. In a large series of patients *(119)*, 41% were noninsulin dependent (40% diet controlled and 60% on sulfonylureas), 46% had experienced secondary failure to sulfonylureas after a mean duration of 9.9 years (range 1–28 years) and 13% were insulin dependent (ketosis prone) from onset. Diabetic micro and macrovascular complications have been reported in these patients. Metformin is not recommended owing to increased risk for lactic acidosis from impaired oxidative phosphorylation.

A distinguishing feature of mitochondrial diabetes is the familial clustering with maternal inheritance pattern as mitochondrial DNA is nearly always transmitted maternally. Another clue to the diagnosis of this form of diabetes is the presence of several associated clinical features such as bilateral sensorineural deafness. This is seen in most patients with A3243G mutation, and, in about half of them, may precede the onset of diabetes. Many patients also have a "pigmentary macular-pattern" retinal dystrophy that is distinct from diabetic retinopathy. It is characterized by atrophy of retinal pigmented epithelium along with subretinal pigment deposits, and does not affect visual acuity. Painful myopathy affecting lower extremities is reported in 40% of patients, with biopsy of skeletal muscles revealing ragged-red fibers typical of mitochondrial myopathy. A few patients with this mutation present with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, a condition referred to as MELAS syndrome. Children with this rare but serious disorder develop deafness and diabetes in their teens.

## DIABETES OWING TO DISEASES OF THE EXOCRINE PANCREAS

Impaired β-cell function and diabetes can result from any process that diffusely injures the pancreas, such as pancreatitis, trauma, infection, surgical resection, or cystic fibrosis. Infiltrative diseases of the pancreas such as hemochromatosis are another cause for diabetes. Focal pancreatic cancer can also cause diabetes by mechanisms other than reduction in β-cell mass *(120)*. Insulin resistance may play an important role in these patients, but most other patients with pancreatic disease and diabetes are profoundly insulinopenic, and need insulin therapy.

## DIABETES OWING TO GENETIC DISORDERS OF INSULIN ACTION: INSULIN RECEPTOR MUTATIONS

Mutations in the insulin receptor gene lead to several syndromes of extreme insulin resistance. Over 50 insulin receptor mutations have been reported and 3 distinct syndromes, Type A Insulin Resistance syndrome, Rabson-Mendenhall syndrome and Leprechaunism (Donohue syndrome) have been described to result from these mutations. The 3 syndromes probably represent different points on the spectrum of receptor dysfunction *(121)* and their salient features are described below.

### *Type A Insulin Resistance Syndrome*

This syndrome was originally described in young, nonobese women with extreme hyperinsulinemia, insulin resistance, acanthosis nigricans, hirsutism, polycystic ovaries, and android habitus *(122)*. The phenotype in affected male subjects is not well characterized. All patients have extreme hyperinsulinemia and marked insulin resistance, but some patients remain euglycemic even after decades of follow up *(123)*. In patients with diabetes, glucose control is usually poor, and microvascular complications are seen at a young age. Normal or low cholesterol and triglyceride levels are reported *(123)*. Extreme hyperandrogenism often requiring total oophorectomy or large wedge resection is a common feature.

Patients with this syndrome typically have heterozygous missense mutations in the insulin receptor gene although homozygous and compound heterozygous mutations are also reported. Mutations in the α subunit generally cause impaired binding or altered processing of the receptor. Mutations in the tyrosine kinase domain of the β subunit cause a more severe, dominantly inherited form of the disease *(124)*. Overall, the degree of insulin resistance is less severe than the two other syndromes, thus accounting for the relatively milder phenotype.

### *Rabson-Mendenhall Syndrome (RMS)*

Patients with RMS have similar features to type A insulin resistance syndrome, such as hyperinsulinism, acanthosis nigricans and hyperandrogenism, but in addition manifest severe growth retardation. Other associated features include dysmorphic facies, pineal hyperplasia, phallic enlargement, and premature dentition. Diabetes mellitus presents between 3 and 7 years of age, and widespread microvascular disease is common even during childhood.

RMS is an autosomal recessive disorder owing to homozygous or compound heterozygous mutations affecting both alleles of the insulin receptor gene *(125)*. These mutations result in severely defective, but not completely absent, receptor activity.

### *Leprechaunism*

Leprechaunism represents the most extreme form of insulin resistance syndrome, and is associated with high mortality. Most affected patients die in infancy, and it has been suggested that this term be restricted to infants or young children less than 2 years of age *(123)*. Affected infants are small for gestational age and grow poorly in the postnatal period, presumably because of lack of insulin action in utero and concomitant defects in various other growth receptors. Dysmorphic features include low set ears, saddle nose, hypertrichosis, loss of sc fat, umbilical hernia and thick lips. Diabetes mellitus may be seen, but fasting hypoglycemia is the major metabolic problem, and is related to severe hyperinsulinemia and defective hepatic glucose release. These patients are glucose intolerant despite having peak serum insulin levels that may be increased as much as 100-fold over normal range.

### *Treatment*

The high morbidity and mortality seen in patients with insulin receptor mutations suggests that current treatment is unsatisfactory. Administration of large doses of insulin is effective in controlling the polyuria and glycosuria, although it may not alleviate the development of diabetic complications. Use of the concentrated insulin solution U500 permits a reduction in volume of insulin administered. Insulin sensitizing drugs have a limited role, although there are instances of some patients responding to metformin treatment alone *(123)*. IGF-1 therapy has been reported to be beneficial *(126,127)*, although not in all patients *(123,128)*. IGF-1 probably stimulates insulin receptors, which do not bind insulin. Leptin therapy has been shown to improve fasting hyperglycemia and hyperinsulinemia as well as glucose tolerance and HbA1c in two siblings with RMS *(129)*. Further studies are necessary to confirm the beneficial effects of leptin therapy in patients with insulin receptor mutations.

## DIABETES OWING TO ACQUIRED INSULIN RECEPTOR ANTIBODIES

Autoantibodies to the insulin receptor cause "type B insulin resistance syndrome," which can lead to another rare "atypical" form of diabetes. The prevalence of this syndrome is not known, but it is clearly quite uncommon. It is predominantly seen in female African American patients, usually in association with systemic lupus erythematosus

or other autoimmune disorders. Some cases have been described in patients with Hodgkin's disease and multiple myeloma. The metabolic manifestations of the syndrome are usually seen after the onset of the underlying autoimmune disease or malignancy.

The clinical features include acanthosis nigricans and features of hyperandrogenism as in other insulin resistance syndromes. Acanthosis nigricans may be quite severe, and besides involving typical areas such as axilla, groin and neck, it is also often seen in the periocular region and lips, which is characteristic of this disease. Although all patients have extreme insulin resistance, the metabolic abnormalities may range from severe diabetes to fasting hypoglycemia, with some patients spontaneously reverting from one extreme to the other. The majority of patients, up to 80% in an NIH case series of 24 patients *(130)*, present with moderate to severe hyperglycemia, which is usually of sudden onset and accompanied by significant weight loss (usually in excess of 10 kg). These patients are usually managed with high doses of insulin, the average reported dose being in excess of 5,000 units/day *(130)*. Despite marked insulin resistance, patients typically have low serum triglyceride levels. Spontaneous remission owing to disappearance of circulating autoantibodies and restoration of euglycemia may be seen in a third of these patients. In patients who receive treatment with either immunomodulatory therapy or plasmapheresis, remission is seen in half. Interestingly, after a prolonged period of hyperglycemia, some patients develop hypoglycemia, which is a poor prognostic indicator, as death often results from intractable hypoglycemia. The cause of this clinical paradox is not clear, but it could involve a fall in autoantibody titer, a change in biologic character of the autoantibody, or a change in insulin receptor production. High dose corticosteroids are effective in the management of hypoglycemia. The benefit of immunosuppressive therapy and plasmapheresis on long term prognosis is not clear.

## DIABETES OWING TO OTHER ENDOCRINOPATHIES

Hyperglycemia or worsening of pre-existent type 2 diabetes may be seen in various other endocrine disorders, which usually cause an increase in the activity of "anti-insulin" hormones. These include syndromes of excess secretion of growth hormone, cortisol, glucagon, thyroid hormone, or catecholamines. Endocrine tumors, which secrete excess amounts of somatostatin and hyperaldosteronemia-induced hypokalemia, can also cause diabetes by inhibiting insulin secretion. A detailed description of these conditions is beyond the scope of this chapter. It is important to consider these endocrinopathies in patients with sudden onset of diabetes, recent worsening, or whose diabetes is difficult to control with traditional measures. Treatment of the underlying endocrine abnormality often leads to resolution of diabetes.

## DIABETES OWING TO DRUG THERAPY

A large number of prescription drugs can lead to hyperglycemia, and modify the onset and presentation of type 2 diabetes. These include drugs that impair insulin secretion such as diazoxide, pentamidine, or α-interferon, and drugs that interfere with insulin action such as glucocorticoids, nicotinic acid, thiazides, and β-blockers. Overt diabetes associated with their use is probably seen only in patients who are already predisposed to develop diabetes, but it is important to recognize their contribution. Avoidance of the offending medication, when possible, may greatly benefit glucose control.

## CONCLUSIONS

Although most patients with type 2 diabetes are typically obese and insulin resistant, some patients exhibit distinctly different phenotypes. Although most of these "atypical" diabetes syndromes are rare, it is important for the clinician to be well acquainted with their features. Often, their recognition requires just a thorough history and physical examination. For example, inspection of the lower extremities and hips for sc fat distribution helps to identify many patients with partial lipodystrophy, which may be more prevalent than previously recognized. Similarly, close attention to family history and presence of associated abnormalities such as deafness will help in the recognition of MODY and mitochondrial diabetes. It is very rewarding to be able to accurately diagnose these patients, as some show a dramatic response to specific therapies, such as leptin-replacement therapy for patients with generalized lipodystrophy and sulfonylureas for certain forms of MODY. Further, these syndromes have helped us to better understand the pathophysiology of type 2 diabetes and design more effective treatment strategies.

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# 28 Diabetes Mellitus Type 2 and Stress: Pathophysiology and Treatment

*Bryan C. Batch and Richard S. Surwit*

***CONTENTS***



**Summary**

Psychological and physical stresses play a significant role in the development of hyperglycemia in the setting of type 2 diabetes. Although Thomas Willis demonstrated hyperglycemia in response to stress as early as the 17th century, results of subsequent animal and human studies are not consistent. This inconsistency exists despite clear physiologic evidence that stress hormones can cause hyperglycemia via modulation of the sympathetic nervous system. Studies, which use both behavioral and pharmacologic interventions to manage stress, offer mixed results regarding the ability of relaxation techniques to modify hyperglycemia. However, when the data are evaluated in the setting of a large meta-analysis, the evidence indicates that modification of stress leads to a modest reduction in hyperglycemia.

**Key Words:** Stress; diabetes; hyperglycemia; sympathetic nervous system; epinephrine.

## STRESS AND HYPERGLYCEMIA: ANIMAL STUDIES HIGHLIGHTING BASIC PHYSIOLOGY AND STRESS RESPONSIVITY

The hyperglycemic effects of stress were noted as early as the 17th century by Thomas Willis *(1)*. The work of Willis was followed in 1849 by that of Claude Bernard *(2,3)*, who demonstrated that lesioning an area of the hypothalamus in normal rabbits causes hyperglycemia, giving early credence to theories that the hypothalamic pituitary axis plays a distinct role in the development of hyperglycemia. In 1930, C.F. Cori *(4)* theorized a link between the physiologic stress response and development of hyperglycemia. In his early experiments with rabbits, Cori demonstrated that initiation of a continuous infusion of epinephrine precipitated hyperglycemia. This effect was reversed once the infusion was ceased.

Unlike Cori, who chose a pharmacologic stress response mechanism, Cannon *(5)* examined the response to a physiological stress, induced by restraining cats in a holder for variable lengths of time. While the cat was in the holder, urine was collected and studied for evidence of glycosuria. Glycosuria was absent at baseline, but developed in animals that were observed to respond to restraint with emotions of fright or rage.

Van Loon *(6)* extended these earlier studies by infusing beta endorphins intracisternally in conscious, unrestrained, adult male rats. He was able to not only demonstrate an increase in plasma glucose precipitated by the infusion, but was able to abolish the effect via adrenal denervation. Disabling neural control of the adrenal gland disrupted the production of cortisol, eliminating the stimulus for the development of hyperglycemia.

Using the C57BL/6J ob/ob mouse model, Surwit et al *(7)* elicited a stress response in both lean C57BL/6J mice and their ob/ob littermates. Although C57BL/6J ob/ob mice were noted to be hyperinsulinemic at baseline, they

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were not noted to be significantly hyperglycemic in the nonstressed state. When stressed, the obese mice had an exaggerated hyperglycemic response compared to lean control animals, associated with a significant reduction in insulin levels. These findings suggested the presence of increased adrenergic sensitivity of the pancreatic islets, possibly explaining the expression of the diabetic phenotype in the obese animals. Further work by Kuhn et al *(8)* demonstrated a marked rise in glucose and suppression of insulin in the C57BL/6J ob/ob mouse as compared to its lean littermates in response to graded doses of subcutaneous epinephrine. A significant shift in the dose response curve to the left was found in the ob/ob mice, confirming increased adrenergic sensitivity of the β cells in these animals. Such data highlighted the role that environmental stress factors may play in the expression of diabetes in the C57BL/6J ob/ob mouse.

Additional studies by Surwit et al *(9)* demonstrated that hyperglycemia and hyperinsulinemia can be induced even in the lean C57BL/6J mouse model with exposure to stress or epinephrine. This response to stress and epinephrine was markedly exaggerated after obesity was induced by feeding the mice a high-fat simple carbohydrate diet. This finding supports the hypothesis that an underlying genetic defect exists in the C57BL/6J mouse that result in a heightened pancreatic β-cell response to adrenergic stimulation, leading to a diminished insulin secretory response and hyperglycemia. This hyper-responsiveness, and consequent hyperglycemia, is exaggerated by obesity.

Additionally, when exposed to stress, the Otsuka Long-Evans Tokushima Fatty rat, another animal model of type 2 diabetes, develops hyperglycemia with increased levels of plasma catecholamines and corticosterone. *(10)*

### *Stress and Hyperglycemia: Human Studies Highlighting Basic Physiology and Stress Responsivity*

Human studies have yielded contradictory results regarding stress stimuli and its effect on blood glucose. A small study by Naliboff et al *(11)* comparing type 2 diabetic subjects and controls showed no change in blood glucose when the intervention group was exposed to psychological stress. Vandenbergh et al *(12,13)* elicited stress responses through the use of hypnosis and electric shock and were able to demonstrate a statistically significant decrease in blood glucose. Alternatively, Goetsch et al *(14)* used mental arithmetic as an acute stressor and were able to demonstrate a hyperglycemic response to stress.

Studies in the Pima Indians *(15)* showed that prediabetic human populations may also show exaggerated glycemic responses to stress. Euglycemic Pima Indians and age matched euglycemic Caucasian controls were given a glucose tolerance test followed by a standard mental arithmetic challenge known to reliably stimulate a sympatho-adrenal response. Although blood pressure and heart rate increased in all subjects during the mental arithmetic challenge, only the Pima subjects showed an elevation in glucose during and following the challenge. The authors postulated that this exaggerated glycemic stress-responsivity may be characteristic of individuals at risk for the development of diabetes. Because of impaired insulin sensitivity and/or disordered beta cell function, prediabetic individuals may be unable to compensate for the glucose mobilizing effects of sympatho-adrenal activation.

Work by Hamburg et al *(16)* highlights the effect that even modest stress can have on glucose homeostasis during a glucose challenge. Small infusions of epinephrine (mimicking the level seen with an upper respiratory viral illness) administered to 7 normal subjects produced minimal changes in the fasting plasma glucose. However, the same infusion of epinephrine produced marked increases in insulin and glucose levels 2 hours after ingestion of 100 g of glucose.

Bruce et al *(17)* compared the sensitivity of type 2 diabetic subjects' response to a norepinephrine infusion with nondiabetic age and weight matched controls. Although norepinephrine caused a rise in plasma glucose in both groups, the plasma glucose response to norepinephrine in the diabetic group was significantly greater.

## Type 2 Diabetes and Stress Management

Both behavioral and pharmacologic mechanisms have been used to reduce stress or modify an individual's response to stress. As early as 1892 Osler identified a common treatment for what he termed "diabetes of obesity," most likely type 2 diabetes, as opiates and rest *(18)*. Animal studies by Borison and Feldberg *(19,20)* using intraventricular injection of morphine showed sustained elevation of blood glucose in cats and rats. This effect was thought to be mediated indirectly by the sympathetic nervous system, as section of the sympathetic ganglia or adrenal ablation caused a reduction in the hyperglycemic response *(21)*.

Giugliano et al *(22)* studied the effect of endogenous opiates on glucose in human subjects with type 2 diabetes. Acute exposure of subjects to 0.5 mg/h of intravenous (IV) beta endorphin led to increased concentrations of insulin and glucagon and decreased plasma glucose levels. Interestingly, Passariello et al *(23)* were able to demonstrate through work with heroin addicts that chronic exposure to opiates resulted in elevated insulin concentrations and reduced insulin secretory response to IV glucose. In retrospect, modulation of hyperglycemia via treatment with opiates by Osler may have modified insulin secretion as opposed to modifying stress response.

Surwit and Feinglos *(24)* published one of the earliest reports of the effects of behavioral anxiolytic therapy on glycemic control in diabetes. They explored the effects of biofeedback-assisted relaxation on glucose tolerance in subjects with type 2 diabetes who were hospitalized on a clinical research ward. A 3-h glucose tolerance test and an intravenous insulin tolerance test were performed on each subject, after which half of the subjects underwent 5 d of a modified version of progressive relaxation training with EMG biofeedback. Exercises for progressive relaxation training were prerecorded on a cassette and practiced by the patient 2 times per day for 5 d. The EMG biofeedback sessions, given for 50 min on 5 separate occasions to subjects in the relaxation group, were designed to give information about muscle tone and assist in the process of relaxation. Thereafter, the treated patients were asked to continue practicing the relaxation techniques 2–3 times a day. After 1 wk, the oral and intravenous glucose tolerance tests were repeated while subjects in the relaxation group continued to practice the relaxation techniques. Relaxation therapy produced significant reduction in incremental glucose area in the intervention group compared to untreated controls. This finding was independent of any effect on insulin sensitivity or increase in insulin secretory activity.

Lammers, Naliboff and Straatmeyer *(25)* investigated the impact of progressive muscle relaxation training on blood glucose and stress levels in 4 insulin-requiring type 2 diabetic patients. Participants were asked to measure levels of daily stress and anxiety using the State Trait Anxiety Inventory (STAI) *(26)* and a subjective scale of tension *(27)* as well as blood glucose levels. Progressive muscle relaxation significantly lowered blood glucose levels in 2 of the 4 subjects over 6 wks. Interestingly, the subjects with the largest response had higher baseline glucose values and worse baseline metabolic control.

Lane et al *(28)* added EMG biofeedback-assisted relaxation training to conventional diabetes intervention, diet modification, and education to assess if there was any added benefit of relaxation training on percent hemoglobin A1c and glucose tolerance. The second objective of the study was to identify characteristics that would predict what subject would respond to relaxation therapy. Thirty-eight volunteers with poorly controlled type 2 diabetes (defined as 2-h post prandial glucose of >200mg/dL) were followed for 48 wk. In the initial phase of the study all subjects underwent measurement of HbA1c, urinary 24-h excretion of glucose, catecholamines, and cortisol, and completion of the Eysenck Personality Inventory (EdITS), the Nowicki Strickland Locus of Control Questionnaire and the STAI. The questionnaires were used to define psychological variables related to stress reactivity.

The initial preliminary testing also included an oral glucose tolerance test (OGTT). In addition, participants underwent intravenous infusion challenge with epinephrine in solution (250 μg EPI, 500mL normal saline, 500 mg ascorbic acid) to assess the effect of epinephrine on glucose and insulin responses to a mixed meal on day 4 before the intervention. On day 5 following the epinephrine infusion challenge, a repeat OGTT was performed after alprazolam pretreatment to evaluate the effect of an anxiolytic on glucose and insulin responses.

This study revealed no significant clinical improvement in HbA1c or incremental glucose area when relaxation training was added to intensive conventional treatment. Although the results suggest that relaxation therapy does not confer added benefit, it is important to interpret these data with the understanding that relaxation therapy may only be beneficial in a subset of patients who are more stress responsive. This theory is supported by the results of the epinephrine and alprazolam responses to glucose in the pretreatment stage of the study. The results show that subjects who had a greater deterioration in glucose tolerance when given epinephrine, and whose glucose tolerance improved with alprazolam, showed greater improvements in glucose tolerance after relaxation training.

Aikens, Kiolbasa, and Sobel *(29)* also applied the concepts of behavioral relaxation training, consisting of progressive muscle relaxation and imagery, in 6 non insulin dependent diabetics who were matched to 6 controls. There was no difference seen between the study or control group's post intervention HbA1c and area under the 2 h oral glucose tolerance curve. Jablon et al *(30)* examined the effect of progressive relaxation training and EMG biofeedback on glucose tolerance (75 g 2-h OGTT), fasting blood glucose, 2-h post prandial blood glucose and fructosamine in an outpatient setting. Twenty subjects with type 2 diabetes were enrolled in a pretest-posttest

treatment versus control group (wait list) design. The participants were given a series of three 20-min audiotapes of relaxation procedures and were asked to practice the tape twice daily. Recordings of electromyographic (EMG) and electrodermal response (EDR) were made during the 2-h OGTT. The results of the study showed that significant improvements were made with regards to stress reduction as measured by the STAI as compared to controls. However, no changes were found in glucose tolerance, fasting blood glucose, 2-h postprandial blood glucose or fructosamine.

Most studies of relaxation therapy have been small, of short duration, and used cumbersome techniques such as EMG-assisted relaxation training. In contrast, Surwit et al *(31)* demonstrated a reduction in HbA1c through the use of a group-administered stress management program. One hundred eight subjects with type 2 diabetes were randomized to participate in a diabetes education program with or without stress management training, consisting of progressive muscle relaxation, instruction in the use of cognitive and behavioral skills to reduce stress levels, and education regarding the health consequences of stress. After a 1 yr follow up period, subjects who received stress management training had a small (0.5%) but significant reduction in HbA1c. Although more than one third of those receiving relaxation showed improvements of HbA1c of 1% or more, there was no significant difference in the effect of baseline trait anxiety scores or interactions with treatment. This latter finding suggests that baseline characteristics such as higher levels of anxiety and stress do not predict glycemic response to relaxation training.

Group based approaches have not consistently been shown to improve diabetes control. A group based counseling program based on the cognitive behavioral therapy approach was described by Karlsen et al *(32)*. In this study of 63 Norwegian adults with both type 1 and type 2 diabetes, cognitive behavioral therapy produced no reduction in the mean HbA1c. However, the overall level of diabetes control before the intervention for both the intervention and control groups left only modest room for improvement in HbA1c, as the mean HbA1c for the intervention group was 7.88% and 8.43% for the control group. Post intervention, the mean HbA1c in the treatment group was 7.99%.

Okada et al *(33)* and Lustman et al *(34)* have explored the use of benzodiazepines to treat hyperglycemia. In an 8 wk randomized controlled trial, Lustman et al studied 58 patients with poorly controlled diabetes who had generalized anxiety disorder or were psychiatrically well (i.e., no extant axis I psychiatric disorder per DSM-IIIR), treating them with either alprazolam or placebo. The target dose of alprazolam was 2.0 mg/d but it is not clear how many patients reached this dose. A statistically significant difference in reduction in HbA1c was seen in the patients who received alprazolam as opposed to those receiving placebo ($-1.1$ versus $-0.3\%$, $p = 0.04$). Surprisingly, the effect seen did not directly correlate with decreases in anxiety.

A recent meta-analysis *(35)* evaluated the use of psychological interventions to enhance glycemic control. The interventions utilized across the 25 trials included individual or group cognitive behavioral therapy, relaxation training, stress management, or group or individual counseling. For the purposes of the meta-analysis, these interventions were classified based on 4 psychotherapeutic models: supportive counseling therapy, cognitive behavioral therapy, brief psychodynamic psychotherapy, and interpersonal psychotherapy.

The main outcome measure recorded in the various studies included in the meta-analysis was long-term glycemic control based on glycated hemoglobin (including HbA1c and HbA1) and/or whole blood, plasma or serum glucose concentrations. According to the authors, standardization methods were used to allow for combination of different measures of the same outcome. They reported use of within- group SD of the differences (change scores) from baseline to follow-up for each outcome to calculate the SE of the effect size for each study. If the SD of the change score was missing, they used the square root of the average of the baseline and follow-up variance in each group. They further stated that their approach was based on the assumption that the correlation between the baseline and the follow-up outcomes values was 0.5. They then standardized the effect sizes by dividing them and their SE by the SD. Secondary outcome measures included body mass index (BMI) and psychological distress. Twelve of the 25 studies included glycated hemoglobin data that could be pooled.

After pooling data from twelve of the trials, the mean percentage glycated hemoglobin (including HbA1c and HbA1) was lower in the people assigned to any psychological intervention than in the control group (standardized pooled mean difference of $-0.32\%$ [95% CI $-0.57$ to $-0.07$]). Improvements in blood glucose, however, were not significant. It is important to note that when 2 studies, in which the control was a less intensive psychological therapy (standard practice or conventional therapy), were excluded the pooled effect size was larger, showing a clinically significant difference in HbA1c of $-1.00\%$.

## SUMMARY

Research in animal and human models has established the effect of the sympathetic nervous system and the hypothalamic pituitary adrenal axis on glucose homeostasis. However, trials employing interventions aimed at stress reduction in human subjects have yielded mixed results with respect to their effect on glucose control. The most comprehensive evaluation of psychological intervention and glycemic control includes a meta-analysis of twelve of the best quality studies utilizing psychological therapies. The results of the meta-analysis suggest that statistically significant improvements in long term glycemic control can be achieved. However, even the best studies included in the meta-analysis were not without flaws in that the studies were often small and the measures used for long term glycemic control were not always equivalent (e.g., HbA1c versus HbA1).

The subset(s) of patients more likely to have improvements in glycemic control when exposed to psychological intervention have thus not yet been defined. Unfortunately, the current literature cannot offer consistent guidelines. A decrease in baseline anxiety and stress over time does not always correlate with changes in glycemic control. This lack of transparency regarding the appropriate patient population to treat makes it difficult to recommend the broad application of psychological interventions in heterogeneous populations of patients with type 2 diabetes. Clearly, more work in this area is necessary.

Considering the above data, use of psychotherapeutic models (supportive counseling therapy, cognitive behavioral therapy, brief psychodynamic psychotherapy, and interpersonal psychotherapy) carries a grade of recommendation of 2B (clarity of risk/benefit unclear) for the purpose of modification of glycemic control in patients with type 2 diabetes.

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# 29 Pharmacologic Factors Affecting Glycemic Control

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***Contents***



**Summary**

Among many challenges to achieving and maintaining glycemic control, the impact of pharmacologic agents on glycemia is a significant, but often overlooked factor. Numerous medications have been implicated in the development of drug-induced hyperglycemia and type 2 diabetes mellitus. Of these, the atypical antipsychotics (for the management of depression and psychosis), the protease-inhibitor anti retroviral agents (for the management of HIV and AIDS), immunosuppressive medications, niacin, and certain antihypertensive agents are the most prevalent. Caffeine is another prevalent, although nonprescription, drug with important metabolic effects. An understanding of the potential effects of these drugs on glucose metabolism is important for the care of patients with type 2 diabetes and for those at risk for the development of diabetes.

**Key Words:** Diabetes; antipsychotics; protease inhibitors; caffeine; beta-blockers, niacin; immunosuppressives.

## INTRODUCTION

The challenges to achieving and maintaining glycemic control come in many forms; the severity and duration of the patient's diabetes, the complexity of the diabetic medication regimen, and patient adherence are major factors. Pharmacologic agents not taken directly for the treatment of diabetes may also interfere with glycemic control. Numerous agents have been implicated in drug-induced hyperglycemia (see Table 1) *(1–4)*. Of these, the atypical antipsychotics (for the management of depression and psychosis) and the protease-inhibitor antiretroviral agents (for the management of HIV and AIDS) have received the most attention recently, although other agents, such as immunosuppressive medications, niacin, and certain antihypertensive drugs may have substantial affects on plasma glucose. Another prevalent, although nonprescription, agent with potentially significant metabolic effects is caffeine. This chapter summarizes the evidence-based literature on the effects of these drugs on glycemia.

## EFFECT OF ANTIPSYCHOTIC AGENTS ON GLYCEMIA

### *Classification of Antipsychotic Agents*

Before 1988, the treatment of psychosis relied on medications, which are now considered "typical," or conventional, antipsychotic agents. These "first-generation" antipsychotics are dopamine-receptor antagonists, including

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Table 1
Sample of pharmacologic agents producing hyperglycemia *(1–4)*

| |
|---|
| Atypical Antipsychotic agents |
| Protease Inhibitors |
| Caffeine |
| Pentamidine |
| Anticonvulsant agents |
| Antineoplastic agents |
| Corticosteroids /Immunosuppressive agents |
| Niacin |
| Thiazide diuretics |
| Beta-adrenergic blockers |

haloperidol, as well as the phenothiazines (e.g., chlorpromazine and fluphenazine), among others. These agents, while effective, are also well-known for the risk of extrapyramidal side effects, including tardive dyskinesia. Newer agents have been developed, with fewer side effects and improved efficacy in treating both positive and negative symptoms of psychosis *(5,6)*. The newer antipsychotic agents, often termed "atypical antipsychotics" or "second-generation" antipsychotics include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole.

## *Glucose Intolerance and Diabetes*

Although the second-generation antipsychotic agents are considered a major advance in the treatment of psychosis, and their use is widespread, multiple case reports, case series, and retrospective studies have established the existence of adverse metabolic effects. Chief among these is the development of glucose intolerance and/or frank type 2 diabetes mellitus. Since the year 2000, several large case series, each including at least 100 reported cases, have documented a significant incidence of both new-onset diabetes mellitus as well as exacerbation of pre-existing diabetes. Of particular concern is the occurrence of diabetic ketoacidosis (DKA), which has been documented with the use of multiple second-generation agents, including clozapine, olanzapine, and risperidone *(7)*. Koller et al have summarized data from the US Food and Drug Administration/MedWatch Adverse Event reporting system, demonstrating that the number of fatal occurrences ranges from 4 to 25 individuals in each case series *(7–10)*.

## *Individual Second-Generation Antipsychotic Agents*

### Clozapine

The association of clozapine use and development of impaired glucose tolerance/diabetes has been demonstrated in numerous case series and retrospective studies. Henderson et al studied 82 patients on clozapine, followed for a total of 5 yr, and found that 36.6% developed type 2 diabetes *(7,11)*. Subsequently, in a 10-yr study of clozapine-treated patients, Henderson et al collected data showing a Kaplan-Meier estimate for new-onset diabetes mellitus of approx 43% over 10 yr *(12)*. Several large database studies have also demonstrated an association between clozapine use and an increased risk of developing diabetes mellitus: the FDA/MedWatch database contains 384 reported cases of diabetes, of which 242 were new-onset (precipitated/unmasked by clozapine), over a 15-yr period, and the VA database showed a significant odds ratio of 1.25 (95% CI 1.07–1.46) for the association between clozapine and diabetes mellitus *(9,13)*. Although the results across the literature are not uniformly consistent—for example, in the Iowa Medicaid database, overall diabetes rates did not differ between those on clozapine and those taking conventional antipsychotics, except in a younger subgroup (age 20–34 yr)—the American Diabetes Association(ADA), the American Psychiatric Association(APA), the American Association of Clinical Endocrinologists(AACE), and the North American Association for the Study of Obesity(NAASO, "the Obesity Society"), published a joint Consensus Statement indicating that the preponderance of evidence shows clozapine is associated with an increased risk of diabetes *(6,7,14)*.

**Table 2**
**Levels of evidence for pharmacologic factors affecting glycemic control**

| *Recommendation* | *Level of evidence* |
|---|---|
| Clozapine is associated with an increased risk of diabetes | 1C+ |
| Olanzapine is associated with an increased risk of diabetes | 1C+ |
| Newer atypical antipsychotics may be associated with the development of glucose intolerance | 2C |
| Protease inhibitor anti-retroviral agents are associated with hyperglycemia and new-onset diabetes mellitus | 1C+ |
| Metformin may improve the cardiovascular risk profile of patients (with HIV/HAART-induced fat redistribution and insulin resistance) via both improved insulin sensitivity and improved fibrinolytic potential | 1B |
| Thiazolidinediones may improve the cardiovascular risk profile of patients (with HIV/HAART-induced fat redistribution and insulin resistance) via improved insulin sensitivity | 1B |
| Caffeine may interfere with postprandial glucose metabolism by an acute decrease in insulin sensitivity. This can produce exaggerated postprandial hyperglycemia in patients with type 2 diabetes. | 2A |
| Caffeine may improve sensitivity to hypoglycemia in type 1 diabetic patients, which might help decrease the number of hypoglycemic episodes. | 2B |
| Corticosteroids, as well as tacrolimus and cyclosporine, have been implicated in new-onset diabetes mellitus in patient who received solid-organ transplantation | 1B |
| Niacin can be considered a viable choice for the treatment of diabetic dyslipidemia, particularly given its benefits in terms of modifying LDL particle size and lipoprotein(a) levels | 1B |
| Certain beta-blocker- or thiazide- based anti-hypertensive regimens are associated with hyperglycemia | 1B |
| Beta-blockers, *as a class,* are associated with hyperglycemia | 2B |

### Olanzapine

Several large database studies, including the VA database *(13)*, the UK General Practice Research Database *(15)*, the Quebec health care database *(16)*, the Blue Cross, Blue Shield database *(17)*, and the FDA/MedWatch database, have shown increased incidence of diabetes (i.e., statistically significant odds ratios from 3.1 to 5.8 for olanzapine versus nonusers of antipsychotics) among patients taking olanzapine *(7,8,13,15–17)*. In a cross-sectional analysis comparing patients with schizophrenia to age-, BMI-, and adiposity-matched nonschizophrenic controls, both olanzapine and clozapine showed statistically significant glucose elevations during glucose tolerance testing at 0 and 75 min *(7,18)*. Based on these and other studies, the ADA/APA/AACE/NAASO Consensus Conference

members concluded that the data are consistent in showing an association between olanzapine and an increased risk for diabetes mellitus. Olanzapine, in combination with fluoxetine used for treatment of depression, has also been associated with significant weight gain (7% or more increase from baseline) *(19)*.

### Other Second-Generation Antipsychotic Agents

Although most authorities agree that olanzapine and clozapine have a preponderance of evidence indicating increased risk for the development of type 2 diabetes, data supporting a similar association with other second generation antipsychotic agents appear to be less consistent. Several retrospective studies have concluded that the use of risperidone does not lead to a significantly increased risk of developing diabetes when compared to patients either on conventional antipsychotic agents or not taking antipsychotics *(7,15,17)*. However, there are case series and other retrospective studies supporting the contention that risperidone can be associated with the development of glucose intolerance and new onset diabetes mellitus *(10,20,21)*, and at least 1 large retrospective cohort study concluded that the risk of developing new-onset diabetes mellitus was greater for risperidone than the conventional antipsychotic haloperidol *(7,22)*. The ADA/APA/AACE/NAASO Consensus Conference members concluded that the risk for diabetes in patients taking risperidone or quitiapine is still "less clear" *(6)*.

Limited data exist for the newest atypical antipsychotics, aripiprazole and ziprasidone. The ADA/APA/AACE/NAASO statement indicated that, at the time of the Consensus Conference in November 2003, clinical trial experience had not shown an increased risk for developing diabetes with these agents *(6)*. However, a case report of new onset diabetes mellitus with ziprasidone has been reported recently *(23)*. This association was not confirmed in a recent VA medical center study of outpatients taking clozapine, risperidone, olanzapine, quetiapine, or ziprasidone; whereas clozapine was associated with occult hyperglycemia, this was not the case for any of the other agents *(24)*.

## *Mechanisms*

The mechanism by which certain second-generation antipsychotic agents may increase the incidence of glucose intolerance remains unclear. There is evidence supporting the development of increased body weight (as well as the development of dyslipidemia) with some of the atypical antipsychotic agents—particularly clozapine and olanzapine *(6,19,25)*. Thus, it is not unreasonable to hypothesize that antipsychotic-induced changes in fat distribution and total weight may increase the risk of developing diabetes. Increased insulin resistance, perhaps owing to competitive binding at insulin receptors or interference with glucose transporter function *(25–28)* may contribute to the problem. In fact, some authorities believe that antipsychotic agents could lead to alterations in insulin sensitivity independent of increases in adiposity *(4)*, and 1 study found that half of the cases of new-onset diabetes reviewed were not associated with weight gain at the time of diagnosis *(7,20)*.

## *Management*

As the evidence grows in support of the association between atypical antipsychotics and metabolic disturbances, there has been increased concern regarding how to manage this issue in the growing population now utilizing these agents. On the positive side, a national survey of psychiatrists revealed that the majority who responded to the survey did recognize that weight gain and diabetes mellitus are important metabolic complications of the atypical antipsychotic agents. Fewer were aware of other metabolic complications such as dyslipidemia and acute hyperglycemia or DKA *(29)*. This survey emphasizes the importance of education and of collaboration among mental health experts, obesity specialists, and diabetologists as the use of atypical antipsychotics continues to expand *(25)*.

The ADA/APA/AACE/NAASO Consensus Statement lists several recommendations regarding baseline screening measures for any patient for whom antipsychotic medication is being considered, including assessment of family history of diabetes or other cardiovascular disease risk factors, BMI, waist circumference, blood pressure, fasting lipids, and glucose. The purpose of these assessments is to identify individuals who may already fit in the diagnostic categories for overweight or obesity, hypertension, or prediabetes, so that treatment can be initiated and specialist care identified, if appropriate *(6)*.

## EFFECT OF PROTEASE INHIBITORS ON GLYCEMIA

### *Clinical Presentations*

The medical treatment of the Human Immunodeficiency Virus (HIV) and the Acquired Immune Deficiency Syndrome (AIDS) has evolved rapidly. Over the past 15 yr, new classes of medications, including protease inhibitors (PI), have been introduced and form the basis for "highly active antiretroviral therapy" (HAART). As PIs gain more widespread use, reports of metabolic complications associated with these agents have become apparent *(30)*.

In the late 1990's, case reports appeared describing HIV-infected patients who, after several months of receiving HAART therapy (including PIs such as indinavir and ritonavir), developed non-ketotic hyperglycemia with no prior history of glucose intolerance *(31)*. Gradually, as more cases of new-onset or worsened diabetes in patients taking PIs accumulated, the FDA elected to issue a Public Health Advisory on the potential for hyperglycemia with the use of protease inhibitors *(32)*.

Although the majority of the case series describe hyperglycemia developing after several months of PI therapy *(31,33–37)*, the timing of onset of symptoms appears to be quite variable, ranging from as early as 2 wks after beginning PI therapy *(38)* up to 1 to 2 yr after initiation of the medication *(30,39,40)*. The clinical presentation can be variable as well, ranging from nonketotic hyperglycemia that is often asymptomatic, to documented DKA *(35,40,41)*. As with the atypical antipsychotics, it is important to recognize the development of DKA as a potentially dangerous complication of protease inhibitor therapy, since the literature includes examples of severe metabolic acidosis (e.g., a patient with a pH of 7.11, bicarbonate of 5 mEq/L, and anion gap of 32) occurring in association with protease inhibitor therapy *(30,40)*.

### *Hyperglycemia Incidence Data*

Multiple cross-sectional studies have attempted to quantify the incidence of glucose intolerance associated with protease inhibitor therapy. Carr and colleagues collected data on 116 patients with HIV whose therapy included at least 1 protease inhibitor, (in addition to data from comparison groups of patients with HIV who remained protease-inhibitor naïve) *(33,42)*. Care was taken to exclude patients on corticosteroids, anabolic steroids, or another treatment which could in itself contribute to the development of impaired glucose tolerance. Impaired glucose tolerance and frank diabetes mellitus were diagnosed via a 75-g oral glucose tolerance test. Although a number of study limitations were noted, including the lack of a controlled comparison for the glucose tolerance data (the formal 75-g test was conducted on most of the patients receiving PIs but on few of the PI-naïve patients), and the nonrandomized nature of the group assignments, the incidence of impaired glucose tolerance was 16% in patients receiving protease inhibitors and the incidence of frank diabetes mellitus was 7%.

Another cross-sectional study compared the incidence of diabetes in HIV-infected patients who were taking PIs with the incidence in those who were PI naïve *(43)*. Of the patients who were PI naïve, none developed frank diabetes, and 24% developed impaired glucose tolerance. However, 13% of the patients who received PI therapy were diagnosed with diabetes mellitus, and 46% developed impaired glucose tolerance *(43)*.

More recently, studies with larger cohorts and longer-term follow-up have been reported *(30)*. One study, of more than 200 HIV-infected patients (of whom 176 were on PI therapy, whereas 45 patients were PI naïve), enrolled the patients over a 5-yr period, with follow-up for at least 6 mo. Hyperglycemia incidence in patients on PI therapy was 2.68 per 100 person-years, whereas the incidence rate for patients who were PI naïve was only 0.65 per 100 person-years, a 5-fold increase with the use of PI therapy *(44)*. Another study of 324 patients with known HIV, but no known diagnosis of pre-existing diabetes, reported that incidence rates for the development of diabetes ranged from 3.6% (with the agent saquinavir) to 14.5% (with the agent indinavir) *(34)*. An even larger cohort study was conducted throughout health care centers in France, by the Antiproteases Cohorte (APROCO) Study Group, involving more than 1000 patients with known HIV. A cross-sectional substudy of 614 of these individuals (APROCO-Metabolic Complications substudy) revealed an incidence rate of 17% for the development of either impaired fasting glucose or impaired glucose tolerance and a 6% incidence rate for the development of overt diabetes mellitus for patients on PI agents (including ritonavir, indinavir, saquinavir, and nelfinavir) *(39)*. A smaller substudy from the APROCO group extended follow-up to 36 mo after initiation of PI therapy, and showed a prevalence of 10% for overt diabetes mellitus at the end of the longer follow-up period *(45)*.

### *Mechanisms*

Early hypotheses suggested that PI induced hyperglycemia resulted from one or more effects on beta-cell function, such as insulin secretion and/or processing defects *(38)*. However, in vitro rodent studies suggested that the pathophysiology is more complicated, and further research identified the development of insulin resistance as another major pathophysiological problem *(46,47)*. Many studies attempting to elucidate the impact of PI on insulin action have focused on insulin-stimulated glucose uptake, specifically, the via the Glut4 glucose transporter. Murata et al. showed that several protease inhibitor agents (indinavir, ritonavir, and amprenavir) significantly inhibited the transport activity of Glut 4 (but not the transport activity of Glut1) *(48)*. Whole animal and human studies later gave this theory further credence, including one randomized, double-blinded, placebo-controlled, cross-over study of the effect of indinavir on glucose disposal in men, showing that a single oral dose of indinavir significantly decreased total and nonoxidative insulin-stimulated glucose disposal *(49,50)*. Woerle et al have noted that mechanisms of dysfunction at multiple levels (beta-cell function, as well as peripheral effects) likely contribute to the pathophysiology *(47,51)*. Others have theorized that PI induced insulin resistance may also result from inhibited expression of peroxisome proliferator-activated receptor (PPAR)-γ *(52,53)*, or that lipotoxic effects of protease inhibitors could underlie the development of peripheral insulin resistance *(53–56)*.

### *Management*

Various options for the therapy of PI induced hyperglycemia have been evaluated *(30)*. Of the oral agents, metformin was one of the earliest to be studied in this setting *(57)*, including randomized, double-blinded, placebo-controlled trials for treatment of insulin resistance in patients on HAART: Hadigan et al showed evidence that metformin may improve the patients' cardiovascular risk profile via both improved insulin sensitivity and improved fibrinolytic potential *(58,59)*. The thiazolidinediones have also undergone considerable scrutiny. Troglitazone was used in a pilot study showing improvements in insulin sensitivity in patients with PI-induced diabetes mellitus, but troglitazone's withdrawal from the market necessitated discontinuation of the study *(60)*. Subsequently, numerous clinical trials have been conducted evaluating the efficacy of rosiglitazone and pioglitazone in the management of the metabolic complications associated with PI use. Although improvements in insulin sensitivity are generally seen, the efficacy of the thiazolidinediones in reversing lipodystrophy is more controversial *(47,61–63)*.

Leow et al have discussed the potential treatment value of 2 important adipocytokines (adipocyte-derived hormones): adiponectin and leptin. Interestingly, the administration of PPAR-γ agonist medications (i.e., thiazolidinediones) has been shown to improve insulin sensitivity in the setting of increased levels of adiponectin. Leptin has been efficacious in the treatment of insulin resistance in leptin-deficient mice, and co-administration of adiponectin and leptin has been considered *(53)*. Although further investigation of these novel therapies is warranted, these options remain purely experimental.

In addition to consideration of pharmacological therapy, preventative measures should be undertaken in at risk patients as well. Lifestyle modification, including regular physical activity and attention to nutrition, is of utmost importance. It is also reasonable to consider periodic screening for impaired glucose tolerance, particularly in patients who remain on PI-containing regimens for prolonged periods of time *(30)*.

## CAFFEINE AND DIABETES

### *Caffeine Pharmacology*

Caffeine is the most popular drug in the world, consumed in coffee, tea, soft drinks, chocolate, and many common medications *(64,65)*. An estimated 90% of the adult population consumes caffeine daily, ingesting amounts that are pharmacologically active *(64,66)*. Daily intake among caffeine consumers in the United States averages about 280 mg, equivalent to 2 to 3 cups of brewed coffee, and estimates are even higher for many European countries *(67)*. Although the scientific literature contains no specific information on the consumption of caffeinated beverages by patients with diabetes, there have been no widespread recommendations against caffeine thus far, and it is reasonable to assume that consumption patterns in diabetic patients are similar to those of the population in general.

Caffeine is known as a stimulant drug, not only for its apparent properties to increase wakefulness and alertness, but because of its widespread stimulatory actions on most of the organ systems of the body, including the central

and autonomic nervous systems, heart and blood vessels, kidney, gastrointestinal system, and respiratory system. Caffeine also stimulates skeletal muscles, increases basal metabolic rate, increases levels of the neurotransmitters norepinephrine and serotonin, and raises plasma and urine concentrations of catecholamines and cortisol *(65)*. Current evidence suggests that the primary mechanism for these effects is competitive antagonism of $A_1$ and $A_{2A}$ adenosine receptors *(68)*. Adenosine receptors are ubiquitous throughout the body and generally serve a regulatory or modulatory function, governing the level of activity and inhibiting excessive levels of activation. Caffeine appears to exert its stimulatory effects indirectly, by blocking this regulatory function, with the result that uncontrolled activity is permitted.

Caffeine is rapidly and completely absorbed after ingestion, appearing in the blood after about 10 min. Peak concentrations are generally reached in 45 to 90 min. Caffeine is metabolized by the liver and the metabolites are eliminated by the kidney, with a typical elimination half-life of 4–6 h. This insures that pharmacologically active caffeine concentrations and resultant physiological effects can persist for many hours after oral ingestion of caffeine in beverages, foods, or medications *(65)*.

Caffeine's effects on the hormones epinephrine and cortisol are probably of greatest relevance to diabetes. It has long been known that caffeine increases levels of epinephrine and cortisol measured in plasma and in urine *(69–72)*. However, caffeine also potentiates catecholamine and cortisol responses to other stimuli, including responses to stressful events in both the laboratory and the natural environment *(71,72)*. Through these counterregulatory hormones, caffeine could exert widespread effects on glucose metabolism and glucose control and play a negative role in the management of diabetes.

### *Caffeine and Glucose Metabolism*

There is a growing body of evidence that caffeine can adversely affect glucose regulation and glucose levels. Studies in the late 1960s and early 1970s found that moderate doses of caffeine, administered as instant coffee, impaired glucose tolerance. The first of these studies *(73)* gave instant coffee or hot water to a small group of male patients with "maturity onset" diabetes before the intravenous administration of a bolus of glucose. The instant coffee produced significantly higher glucose levels throughout the 60 min of the test. A similar test was conducted in a group of third-trimester pregnant women, and again instant coffee was associated with impaired glucose tolerance and slower glucose disposal following intravenous glucose administration *(74)*. Two studies of healthy normal volunteers yielded contradictory results. One study that used an intravenous glucose tolerance test found the same higher glucose levels and slowed glucose disposal after "nondecaffeinated" instant coffee compared to decaffeinated instant coffee *(75)*. However, a second study that used a 3-h oral glucose tolerance test did not find impaired glucose tolerance after instant coffee, but rather found lower postprandial glucose levels in the first hour *(76)*. Subjects in these studies consumed 2 cups of instant coffee that contained an estimated 200 to 400 mg of caffeine, which is a moderate dose for regular coffee drinkers. Despite the evidence that caffeine could have an adverse effect on glucose metabolism, this line of research was not immediately pursued.

More recent studies have investigated the effects of caffeine on insulin sensitivity. Five studies have found that caffeine acutely decreases insulin sensitivity in healthy men. These studies have used both oral glucose tolerance tests and hyperinsulinemic-euglycemic clamp procedures. Caffeine was generally administered at a moderate dose of 5 mg/kg, which provides a 70 kg man a dose roughly equal to 24 oz (700 mL) of brewed coffee. Results are consistent across the studies with regard to evidence for decreased sensitivity to insulin. Studies that use the oral glucose tolerance test find that caffeine increases postprandial concentrations of insulin or C-peptide, usually without a change in the glucose response during the test *(77–79)*. Clamp studies find that caffeine decreases whole-body glucose disposal, which indicates a decrease in sensitivity to infused insulin *(80,81)*.

Results to date suggest that caffeine's antagonism of insulin is mediated by elevated epinephrine rather than by peripheral antagonism of adenosine. Several of these studies noted that caffeine administration increased epinephrine levels during testing *(79–81)*, and blockade of beta-adrenergic receptors with propranolol abolished caffeine's effect on insulin *(79)*. In contrast, administration of an adenosine reuptake blocker did not affect insulin sensitivity *(81)*.

In these studies of healthy individuals, caffeine did not produce significant exaggerations of the postprandial glucose response in the glucose tolerance test, as had been reported earlier. These healthy individuals may have had sufficient pancreatic insulin reserves to overcome the transient decreases in insulin sensitivity, which enabled

them to maintain normal glucose responses to the carbohydrate load during the test. However, individuals who have type 2 diabetes might not have adequate insulin reserves and could be expected to demonstrate an exaggerated postprandial glucose response, as insulin sensitivity decreased when caffeine was consumed before a meal. This hypothesis has been confirmed in at least 3 studies.

The first study *(82)*, compared a moderate dose of caffeine (375 mg) versus placebo for their effects on glucose and insulin responses to a mixed-meal containing 75 gm of carbohydrate (Boost™) in a group of 14 type 2 diabetic men and women who drank 2 or more cups of coffee daily. Caffeine did not change fasting levels of glucose or insulin before the meal. However, caffeine produced a 21% increase in the glucose response to the meal, assessed by the area under the 2-h glucose concentration time curve ($AUC_{2HR}$). The insulin $AUC_{2HR}$ was increased by 48%. Similar results were found in a second study of 12 type 2 diabetic men, who completed a 3-h oral glucose tolerance test (OGTT) after ingestion of caffeine (5 mg/kg) or placebo. Caffeine increased the glucose AUC by 16%. The insulin AUC was 25% greater after caffeine, and serum insulin, proinsulin, and C-peptide concentrations were all significantly higher. In both studies, postprandial glucose excursions were potentiated by caffeine, despite the higher levels of insulin that were observed. These diabetic subjects were unable to overcome the increase in insulin resistance and consequently demonstrated an exaggerated hyperglycemic response when caffeine was ingested before the carbohydrate load.

Following publication of these studies of caffeine, other research raised questions about the possible protective effects of other compounds in coffee that might be beneficial for those with type 2 diabetes *(83–88)*. Because coffee is the largest source of dietary caffeine, it was crucial to determine whether these other compounds prevented the caffeine-related hyperglycemia. A third study was conducted in which caffeine was administered in decaffeinated coffee and decaffeinated coffee served as the control *(89)*. Twenty type 2 diabetic men and women, who were regular coffee drinkers, completed 2 mixed-meal tolerance tests. Once again, administration of caffeine elevated postprandial glucose (by 28%) and insulin (19%), despite the presence of the other chemical constituents present in brewed coffee.

These studies provide strong evidence that caffeine has adverse effects on postprandial glucose in patients with type 2 diabetes. Apparently, regular intake does not lead to tolerance to these effects, because the subjects who demonstrated these effects all drank moderate to large amounts of coffee daily. The caffeine effects were present after only overnight caffeine abstinence, which is what coffee drinkers experience every day. It is quite likely that similar postprandial effects occur every day that a type 2 patient consumes caffeine. Exaggeration of postprandial glucose responses will contribute to higher average glucose levels. Thus, caffeine consumption may disrupt clinical efforts at glucose control in patients with type 2 diabetes and increase risk of complications. Although the question of caffeine's clinical impact does not yet have an empirical answer, prudence would suggest that patients with type 2 diabetes be advised to abstain from caffeinated beverages, foods, and medications to eliminate the effects of caffeine that could worsen their disease. The value of this simple lifestyle change could be assessed on an individual basis.

### *Caffeine and Sensitivity to Hypoglycemia*

In sharp contrast to the detrimental effects that caffeine may have on glucose control in type 2 diabetes, some investigators have suggested that caffeine use may be beneficial for those with type 1 diabetes. The results of several studies suggest that caffeine administration exaggerates perception of the symptoms of hypoglycemia in both healthy nondiabetic individuals and in patients with type 1 diabetes.

A study of healthy non-diabetic individuals *(90)* used a hyperinsulinemic glucose clamp technique to maintain constant glucose levels in the normal, low normal and hypoglycemic range after administration of a moderately high dose (400 mg) of caffeine or placebo. When caffeine was ingested, the healthy subjects were more aware of hypoglycemic symptoms and reported them even when glucose was maintained at low-normal, but not hypoglycemic, levels. Caffeine also potentiated the counterregulatory hormone responses (epinephrine and cortisol) to mild and moderate hypoglycemia. The authors cautioned that this could increase complaints of hypoglycemic symptoms in healthy individuals who drink coffee, whenever glucose falls to low-normal levels, as it would after a significant carbohydrate load. Similar effects were observed in patients with type 1 diabetes *(91)*, who provided stronger symptom reports and larger counterregulatory responses when glucose was lowered after caffeine administration. Here the exaggerated symptoms were seen as a potential benefit of caffeine consumption

that might protect type 1 patients from otherwise asymptomatic episodes of hypoglycemia and reduce the risks of neuroglycopenia associated with intensive glucose management. Caffeine administration could serve a protective function by warning the diabetic individual of falling glucose levels before the hypoglycemic state appeared.

A study of free-living type 1 diabetic patients tested the hypothesis that caffeine would reduce episodes of hypoglycemia when used chronically *(92)*. Daily administration of 400 mg per day of caffeine was associated with an increased frequency of mild symptomatic episodes of hypoglycemia (confirmed by self-monitored blood glucose) over a 3-mo period, compared to a placebo control, but did not reduce the number of asymptomatic episodes. Chronic glucose levels ($HbA_{1c}$) were not affected by treatment. Although results suggest that caffeine might be increasing the likelihood that episodes were detected (and could be responded to), the study could not rule out the possibility that caffeine actually made hypoglycemia more likely. The hypothesis was tested again when type 1 patients were given moderately high caffeine doses (500 mg per day) or placebo for 2-wk periods, and a continuous glucose monitor assessed interstitial glucose levels for the last 48 h of the interval *(93)*. Caffeine was associated with a lower frequency of moderate hypoglycemic episodes (interstitial glucose level < 54 mg/dl for at least 20 min), a reduction observed only during nighttime hours, but an increased frequency of mild episodes. Results from these studies raise questions about the usefulness of caffeine for prevention of hypoglycemia in type 1 diabetes. Enhanced awareness of symptoms may reduce the likelihood of a hypoglycemic episode, but might also lead to an increased reluctance to keep glucose levels under tight control. Furthermore, the potential for other adverse effects from long-term consumption of moderate to high daily doses recommends against this intervention in clinical diabetes management, at least until more supportive evidence of value might become available.

### *Caffeine: Conclusions*

Despite the fact that research on caffeine and diabetes began over 35 yr ago, there are still no final answers to questions about the possible adverse effects or benefits that consumption of caffeinated beverages and foods may have for patients with diabetes. However, given the likely prevalence of caffeine consumption in the diabetic population, these questions have enormous public health importance. Only when the effects of caffeine on glucose management in diabetes are clearly understood should widespread recommendations about caffeine use be developed and disseminated. In the meantime however, individual patients may derive benefit from a greater appreciation of the effects of caffeine. Type 2 patients especially may be encouraged to determine for themselves whether the elimination of caffeine from the diet leads to improvements in glucose levels and personal diabetes management.

## EFFECT OF IMMUNOSUPPRESSIVE AGENTS ON GLYCEMIA

### *Solid Organ Transplantation - General*

The development of post-transplant diabetes mellitus (PTDM) and/or impaired glucose tolerance in solid organ transplant recipients is a well-known medical problem. The registry of the International Society for Heart and Lung Transplantation has indicated that diabetes mellitus is found in as many as 32% of heart transplant recipients because of a combination of risk factors, which include both pretransplant diabetes and the development of new-onset diabetes owing to the effect of immunosuppressive agents *(94–96)*. Recognition of this problem led to the creation of an International Expert Panel that developed guidelines for the diagnosis, treatment and management of PTDM *(97,98)*. However, much of the evidence-based literature on the relationship between immunosuppressive agents and PTDM comes from studies of renal transplantation.

### *Solid Organ Transplantation—Renal*

Effective use of immunosuppressive agents is fundamental to the success of graft survival after renal transplantation. However, renal transplant patients are at risk for new-onset post-transplant diabetes mellitus. Using the criteria for the definition of PTDM, (defined at the International Diabetes Federation's Expert Panel Meeting *(97,98)* ), Sulanc et al performed a retrospective study of adult renal transplant (living or cadaveric donor) patients, 61 of whom received transplants during the years 2001–2003, and another 61 of whom received transplants from 2000 to 2001, taking into account the fact that immunosuppressive regimens before 2001 were more likely to

include corticosteroids. The authors found that both groups had a notably high percentage of patients developing PTDM (74% in the 2001–2003 group and 56% in the 2000–2001 group) within 1 yr after transplantation *(99)*. However, when multivariate analyses were performed, accounting for confounding factors such as ethnicity, BMI, and immunosuppressive therapy, there was no significant difference in the incidence of PTDM between the 2 groups, implying that even immunosuppressive regimens not including corticosteroid agents still put patients at high risk for PTDM *(99)*.

Besides corticosteroids, other immunosuppressive agents implicated in new-onset diabetes mellitus include tacrolimus and cyclosporine (cyclosporin A). Corticosteroids, as well as tacrolimus and cyclosporine, are thought to contribute to hyperglycemia through a variety of mechanisms, including the inducement of insulin resistance coupled with direct beta cell effects *(100)*. The differential impact of individual immunosuppressive agents on incidence of PTDM and glycemic control has been examined. Bouchta et al studied 34 patients who developed PTDM following renal transplantation and were converted from tacrolimus to cyclosporine, with 32 followed for 12 mo postconversion. At 12 mo, the authors found a statistically significant reduction in fasting plasma glucose and HbA1c levels ($6.8 \pm 0.8\%$ versus $6.0 \pm 0.6\%$, $p < 0.001$) *(101)*. Araki et al compared immunosuppressive regimens including mycophenolate mofetil or azathioprine and corticosteroids in combination with cyclosporine (Group I), tacrolimus (Group II), or sirolimus (Group III) and found a PTDM incidence of 7.6%, 11.7%, 5.9% respectively over an average of 39 mo follow-up in 528 renal transplant patients; these differences were not statistically significant *(102)*. However, Ciancio et al performed a 3-yr analysis in which 150 renal transplant recipients were randomized to tacrolimus and sirolimus (GroupA), tacrolimus and mycophenolate (GroupB), or cyclosporine and sirolimus (GroupC). They found the incidence of new-onset diabetes to be 27%, 11%, and 31% respectively ($p = 0.09$), although a comparison of Group B to Groups A and C combined did reveal a significant difference ($p = 0.04$) in favor of the tacrolimus and mycophenolate group *(103)*. Additional studies are ongoing *(104)* in order to further clarify the differential effects of the various immunosuppressive agents on PTDM.

Several groups have explored both predisposing factors contributing to immunosuppressive-induced PTDM and methods to reduce its incidence. Predisposing factors include age, African-American or Hispanic ethnicity, and possibly baseline obesity (pretransplant BMI) *(99,100,105)*. Novel strategies aimed toward reduction in PTDM incidence include cytomegalovirus(CMV) prophylaxis and statin use *(100,106,107)*.

## NIACIN AND DIABETES

Despite the potential cardiovascular benefits resulting from increasing HDL-cholesterol with niacin therapy, there have been expressions of concern about the use of niacin in patients with diabetes. This concern is understandable given the demonstrated association between niacin and the development of modest to severe hyperglycemia *(108)*. However, the ADMIT study, and a number of subsequent studies, have proposed that niacin be considered a viable choice for the treatment of diabetic dyslipidemia, particularly given its benefits in terms of modifying LDL particle size and lipoprotein(a) levels *(109–111)*.

The ADMIT study included 468 participants who had known peripheral arterial disease, of whom 125 also had a diagnosis of diabetes mellitus. Participants were randomized to receive niacin (crystalline nicotinic acid up to 3,000 mg/d) versus placebo. Of the diabetic patients, 64 were randomized to niacin and 61 to placebo. Although niacin significantly increased HDL-cholesterol (by 29%), glucose levels also significantly increased (by 8.1 mg/dL) in patients with diabetes over the period from baseline to a time derived from the mean of 6 postrandomization follow-up measurements up to 60 wks. However, the HbA1c levels of participants with diabetes who were taking niacin were unchanged from baseline to mean follow-up (7.8–7.8%, respectively). With regard to medication use, required to maintain this HbA1c, insulin use went up by 13% in those with diabetes on niacin, versus 4% in those on placebo, but this difference was not statistically significant. Furthermore, there was no significant change in the use of oral hypoglycemic agents as a result of niacin therapy ($p = 0.94$). Overall, the authors concluded that niacin could be used for lipid therapy in patients with stable, controlled, type 2 diabetes, with the caveat that this study does not preclude a possible adverse effect of niacin on glycemic control if higher doses are used *(109)*.

Pan et al subsequently published a study using a different approach to the management of niacin use in patients with diabetes. Rather than aiming for hemoglobin A1c stability, along with minimal changes in insulin or oral

agent dosing (as in ADMIT), this group chose to actively increase oral hypoglycemic or insulin dosages in order to allow upward titration of extended-release niacin in 36 diabetic participants, resulting in a significant decrease in mean HbA1c from 7.5% to 6.5%, even in the setting of extended-release niacin doses from 1,000–4,000 mg daily *(110)*. However, given the aggressive medication titration approach, patients who accomplished a >1% reduction in HbA1c did so in the setting of considerable additional pharmacologic management (with oral agents and/or insulin). This study is limited by its open-label, uncontrolled, nonrandomized approach.

In contrast to the above, ADVENT (Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial) was a 16-wk, multicenter, double-blind, placebo-controlled, randomized trial, which assigned 148 patients to 1 of 3 groups: placebo, extended-release (ER) niacin 1,000 mg daily, or ER niacin 1,500 mg daily *(111)*. (Forty-seven percent of the patients were also on statin therapy.) Dose-dependent increases in HDL-cholesterol (significant versus placebo) occurred in both niacin groups. The baseline to week 16 HbA1c values for placebo, ER niacin 1000mg, and ER niacin 1,500mg, were 7.1–7.1%; 7.3–7.4%; and 7.2–7.5%, respectively. The change in HbA1c from baseline to week 16 was significantly different compared to placebo ($p = 0.048$) in the ER niacin 1,500 mg group, and was not significantly different in the ER niacin 1,000 mg group. "Investigator-subjective assessments" of diabetes control and medication use showed that more adjustments were made for patients in the ER niacin 1,500 mg group than in the 1,000 mg group *(111)*. Overall, the authors concluded that low doses of ER niacin are a viable treatment option in patient with type 2 diabetes, and noted the similarity of these findings to that of the earlier ADMIT study.

With regard to cardiovascular outcomes, Canner et al published an analysis by glycemic status of the Coronary Drug Project, a 1974 study that demonstrated significant risk reduction in cardiovascular events and total mortality with niacin *(112–114)*. Canner et al's analysis showed that niacin's beneficial effects on cardiovascular events and total mortality were maintained even in the subgroup of patients who showed the largest increase (from baseline to 1-yr follow up) in fasting or 1-h plasma glucose *(115)*.

## EFFECT OF ANTIHYPERTENSIVE AGENTS ON GLYCEMIA

### *Beta-Adrenergic Blockers*

Studies addressing the relationship between beta-adrenergic blockers and the incidence of hyperglycemia and/or new-onset diabetes mellitus are fairly prevalent throughout the recent literature. As an example, the LIFE study (Losartan Intervention for Endpoint reduction in hypertension study) compared an antihypertensive regimen containing the angiotensin-II receptor blocker losartan with a regimen containing the beta-adrenergic blocker atenolol. LIFE was a large randomized trial involving over 4000 patients in each group. The overall conclusion from the study was that losartan was superior for several reasons. These included greater prevention of cardiovascular morbidity and mortality compared to atenolol as well as a significantly lower incidence of new-onset diabetes: 6% with losartan versus 8% with atenolol. It should be noted, however, that the study also involved the use of a possible confounding factor: thiazide diuretics. Hydrochlorothiazide was an optional part of the antihypertensive regimen in both arms of the study *(116)*.

Several other large trials have also found a higher incidence of new-onset diabetes when beta-blocker-based antihypertensive regimens were compared to angiotensin-converting enzyme inhibitors (e.g., the Captopril Prevention Project, CAPPP) or to calcium channel blockers (e.g., the International Nifedipine GITS study, INSIGHT; the International Verapamil-Trandolapril Study, INVEST; the Anglo-Scandinavian Cardiac Outcomes Trial, ASCOT) *(117–121)*. These studies appear to imply a consistent association between beta-blocker-based antihypertensive regimens and hyperglycemia, but are limited in that the regimens often included concomitant use of a thiazide diuretic as well.

Several of the most recent studies of antihypertensives and incident diabetes further support this association. Thornley-Brown et al studied the effects of an angiotensin converting enzyme(ACE)-inhibitor (ramipril), a calcium channel blocker (amlodipine), and a beta-blocker(metoprolol) on the incidence of diabetes and impaired fasting glucose(IFG) in African-American patients with hypertensive kidney disease. The authors found that the incidence of new-onset diabetes was 2.8%, 4.4%, and 4.5% per patient-year, respectively, for ramipril, amlodipine, and metoprolol; the incidence of IFG or diabetes was 11.3%, 13.3%, and 15.8% per patient-year, respectively *(122)*. Taylor et al performed a prospective study of 3 major cohorts, including the Health Professionals Follow-up

Study, the Nurses' Health Study I, and the Nurses' Health Study II, evaluating the effect of antihypertensive medications on new-onset diabetes. Besides inclusion of these large cohorts, this study's strength included its analysis, which adjusted for confounding factors such as age, BMI, and physical activity *(123)*. The results demonstrated a multivariate relative risk of 1.32 (1.20–1.46) in older women, and 1.20 (1.05–1.38) in men for the development of new-onset type 2 diabetes in those taking beta-blockers as compared to those who did not *(123)*.

Finally, even with this preponderance of evidence, to consider the glycemic effects of beta-blocker agents as a class would be an oversimplification. For example, carvedilol has been shown to have little to no detrimental effect on glycemic control, whereas metoprolol has been associated with a significant increase in mean HbA1c *(124)*.

### *Other AntiHypertensive Agents*

There is also evidence supporting a similarly increased risk for the development of diabetes with the use of thiazide diuretics *(121,123,125)*. For example, the large cohort study by Taylor et al also showed a multivariate relative risk of 1.20 (1.08–1.33) in older women, 1.45 (1.17–1.79) in younger women, and 1.36 (1.17–1.58) in men for developing new-onset type 2 diabetes in those taking a thiazide diuretic as compared to those who did not *(123)*.

Finally, unlike thiazide and beta-blocker agents, other commonly used antihypertensive agents, specifically ACE-inhibitors, angiotensin II receptor blockers, and calcium channel blockers, have not generally been associated with detrimental effects on glycemic control *(116,121–123)*.

## CONCLUSION

In summary, multiple pharmacologic agents have been associated with the development of hyperglycemia and new-onset diabetes mellitus. These drugs are used to treat diagnoses across a broad array of medical subspecialties, including infectious disease, cardiology/hypertension, as well as psychiatry. Given the broad applicability of these medications, it is important to recognize and monitor for potentially detrimental effects on glycemia, to improve the care of patients with known type 2 diabetes and those at risk for the development of diabetes mellitus.

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# 30 Influencing Self-Management: From Compliance to Collaboration

*Martha M. Funnell and Robert M. Anderson*

***CONTENTS***



**Summary**

Greater understanding of diabetes and its treatment, new technology and improved therapies have dramatically changed the clinical care of diabetes. Unfortunately, implementing newer evidence-based findings for understanding and impacting self-management and diabetes self-management education has not kept pace. Much of what we do is based on traditional beliefs and methods that are simply not effective. To effectively influence diabetes self-management, we must begin to move from lecturing to listening and compliance to collaboration.

**Key Words:** Patient education; patient empowerment; self-directed goal setting; chronic care model.

## INTRODUCTION

More than any other chronic illness, diabetes is a self-managed disease. Because patients provide at least 99% of their own care, the implementation of provider recommendations and ultimately their outcomes are largely in their hands. This responsibility cannot be negotiated, assigned, or diminished. *(1)* Although this has been recognized for many years, the dilemma has been what to do about it. A multitude of strategies have been developed, evaluated and promulgated in an attempt to address this issue, including various patient education methodologies, behavioral strategies to promote compliance and professional education to enhance the communication skills of providers. Although many of these have produced modestly successful results, none have provided the ultimate answer for influencing patient self-management.

There is convincing evidence *(2)* that each of the components identified above is essential, but not sufficient for effective self-management. In addition, integrating these strategies into the broader context of a collaborative model of care is more effective than attempts to use any particular strategy. Self-management therefore has the potential to change the way the roles of patients and health care professionals are defined and care and education are delivered. This review focuses on recent efforts to study interventions designed to integrate strategies to educate and empower patients for informed decision-making, assist patients to achieve and sustain self-directed behavioral changes, and ultimately to modify systems of care to influence patient self-management.

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## DIABETES SELF-MANAGEMENT

Diabetes self-management refers to all of the activities in which patients engage to care for their illness, promote health, augment physical, social and emotional resources and prevent the long and short-term effects from diabetes. Self-management is defined as the tasks patients need to undertake to live well with a chronic disease such as diabetes. It includes the ability, knowledge, skills and confidence to make daily decisions, select and make behavior changes and cope with the emotional aspects of their disease within the context of their lives. *(3,4)*

Although diabetes self-management is essential for diabetes care, it is demanding, complex and difficult to sustain. When patients make different self-management choices than the recommendations of their providers it is a source of concern and frustration. This issue has been primarily described in the literature as patient noncompliance. Most of the research in this area in diabetes has focused on understanding its causes to develop interventions to modify patients' self-management decisions to bring them in line with their provider's recommendations. Although widely accepted, this concept is problematic. *(5–8)* There are more than 1,500 articles on compliance in the diabetes literature, none of which have offered a consistently effective approach for resolving this problem. In addition, accurate measurement of compliance requires that the exact recommendations given to patients by their provider are known. Furthermore, it assumes that recommendations given to patients are understood and are consistent from patient to patient and provider to provider.

Over the past 15 yr, diabetes care providers and researchers have questioned the usefulness of compliance as a conceptual framework to understand and influence the self-management behavior of patients with diabetes. *(5–8)* Research in this area has led to the realization that the problem defined as noncompliance in diabetes results from defining the roles, responsibilities and expectations of patients and health care providers in diabetes care as they are defined in the treatment of acute illness. *(9)*

The DAWN study *(10)* reported that only 46% (2–63% range) of patients with type1 diabetes and 39% of patients with type 2 diabetes reported achieving success in two-thirds of their self-management domains. Patient reports of self-management success for medication adherence (overall range 78–83%) and glucose monitoring (64–70%) were much higher than for diet (37–39%) and exercise (35–37%). Both patients and providers reported that a majority of patients suffer from psychosocial problems that interfere with their diabetes self-management. The difficulty patients have making and sustaining lifestyle changes involving diet and exercise puts increased emphasis on the importance of medication use.

A recent review of the research related to medication use reported that rates of taking blood-glucose lowering agents ranged from 65% to 85% with lower rates (36–54%) reported for certain populations (e.g., Medicaid recipients) and regimens requiring more frequent dosing *(11)*. There were a number of reasons cited for lower rates including patients' inadequate understanding of the regimen, medication side effects, lack of perceived regimen benefits, medication costs, and regimen complexity *(12)*. Developing a trusting relationship and addressing noncost issues related to medication use *(13)*, assessing medication cost pressures *(14)* modifying regimens, explaining the importance of each medication, providing information on sources of low-cost drugs and linking patients with coverage programs *(15)* can all help to address the problem of medication underuse.

## INFLUENCING SELF-MANAGEMENT: DIABETES EDUCATION

Diabetes self-management education (DSME) has been considered one of the cornerstones of diabetes care since the advent of insulin, when diabetes truly became a chronic disease. Because of the history of nursing in the area of patient education beginning with Florence Nightengale, Eliot P. Joslin hired and trained diabetes teaching nurses in the 1930s. These nurses were the true pioneers in the field of diabetes patient education *(16)*.

Although for many years patient education was acknowledged as part of diabetes care, very little was known about its effectiveness. It was generally assumed that telling patients what they should be doing would result in behavior change. The success of patient education was judged by the patients' ability to be compliant with their treatment program. Education was largely content-driven and the primary educational strategy was lecturing to patients. The view was that patients should learn what to do and then adapt their lives to fit the recommendations of their health care professionals. It was not until the 1960s that a significant amount of research was done in this area. Three comprehensive reviews of the patient education literature in chronic disease documented for the first

time that 1) any formal education provided is better than none and 2) behaviorally oriented patient education is significantly more potent than didactic education *(17–19)*.

Unfortunately, 2 studies conducted specifically among patients with diabetes [one published in 1961 *(20)* and another in 1983 *(21)*] concluded that glycemic control was not improved through patient education. These findings sparked much debate until the publication of multiple meta-analyses documenting the effectiveness of diabetes self-management education for improving metabolic and psychosocial outcomes *(22–24)*. Results of subsequent meta-analyses are similar to both the early and the later meta-analyses *(4,25–30)*.

Generally, the meta-analyses have documented that DSME interventions have a positive effect on diabetes-related health and psychosocial outcomes, specifically, increasing diabetes-related knowledge, and improving blood glucose monitoring, dietary and exercise habits, foot care, medication, coping, and glycemic control *(4,25–30)*. Although the evidence supports the efficacy of DSME programs as a whole, variability in program goals, outcome measures, length of intervention, number and frequency of sessions, learning format, and demographic make-up of participants means that it is not possible to define an optimal DSME program *(25,28)*.

In spite of the limitations cited, these meta-analyses document not only the effectiveness of self-management education, but also provide some insights into the efficacy of various educational approaches and strategies. Most report that although no one specific educational intervention is superior to another, programs that incorporate the behavioral and affective components along with the clinical *(25,28,31–33)* appear to produce better outcomes. Tailoring the intervention to the age and culture of the participants and including spouses and adult children may also increase DSME effectiveness, as has been shown for older African-American and Latino individuals with diabetes *(29)*. Table 1 summarizes characteristics of effective interventions in clinical and nonclinical settings.

National Standards for Diabetes Self-management Education were first established in 1982 and have been reviewed and revised every 5–10 yr since that time. Extensive literature reviews were completed and provided the evidence for revising these standards in 2001 *(34)* and again in 2007 *(35)*. These standards form the basis for the American Diabetes Association (ADA) Education Program Recognition process. Content areas identified by these

**Table 1**
**Effectiveness of diabetes self-management education**

| |
|---|
| Characteristics of effective interventions |
| • Regular reinforcement is more effective than one-time or short-term education. |
| • Patient participation and collaboration appear to produce more favorable results than didactic interventions. |
| • Group education is more effective than one-on-one education for lifestyle interventions and appears to be equally effective for improving knowledge and accuracy of SMBG. |
| • Studies with short-term follow-up are more likely to demonstrate positive effects on glycemic control and behavioral outcomes than studies with longer follow-up. |
| Effectiveness in clinical settings |
| • In the short term (<6 mo), DSME improves knowledge levels, SMBG skills, and dietary habits (per self-report). |
| • In the short term (<6 mo), glycemic control improves. |
| • Improved glycemic control does not appear to correspond to measured changes in knowledge or SMBG skills. |
| • Weight loss can be achieved with repetitive interventions or with short-term follow-up (<6 mo). |
| • Physical activity levels are variability affected by interventions. |
| • Effects on lipids and blood pressure are variable but are more likely to be positive with interactive or individualized, repetitive interventions. |
| Effectiveness in nonclinical settings |
| • Some evidence indicated that DSME is effective when given in community gathering places (e.g., churches, community centers) for adults with type 2 diabetes. |
| • The literature is insufficient to assess the effectiveness of DSME in the home for adults with diabetes. |
| • The literature is insufficient to assess the effectiveness of DSME in the worksite. |

Reprinted with permission. Norris 2003; Practical Diabetology *(31)*

Table 2
Recommended diabetes self-management content areas

- Describe the diabetes disease process and treatment options.
- Incorporate nutritional management into lifestyle.
- Incorporate physical activity into lifestyle.
- Use medication(s) safely and for maximum therapeutic effectiveness.
- Monitor blood glucose and other parameters and interpret and use the results for self-management decision making.
- Prevent, detect, and treat acute complications.
- Prevent, detect, and treat chronic complications.
- Develop personal strategies to address psychosocial issues and concerns.
- Develop personal strategies to promote health and behavior change.

Adapted from Funnell, 2007; Diabetes Care *(35)*

standards are outlined in Table 2. In addition to these content areas, the Standards established standards across 3 domains: 1) program structure, 2) program process, and 3) program outcomes. Program structure addresses organization-based needs assessment, management, staff, curriculum and access for participants. Program process addresses assessment and methods for implementation of DSME. Program outcomes address continuous quality improvement, program-focused outcome evaluation, and participant-based outcome evaluation. The development of evidence-based standards and the ADA Recognition process facilitated the passage of the Balanced Budget Act and legislation in 46 states to provide reimbursement for DSME through Medicare, Medicaid and other insurance companies.

The literature is divided on the overall effectiveness of group versus individual methods *(26,33,36)*. Norris et al *(26)* found no differential impact between individual and group-based interventions for improving glycemic control and Rickheim et al *(37)* found slightly greater improvements in A1C among patients randomly assigned to a group education condition, when compared with the group assigned to individual education. Another review by Deakin et al *(33)* found that among patients diagnosed with type 2 diabetes, group-based education was effective for improving fasting blood glucose and A1C levels, systolic blood pressure, body weight, need for medication, and diabetes knowledge. The effects may be more positive for group delivery of lifestyle programs (for example those that involve diet and physical activity) *(36)*.

Teaching self care skills has been found to be effective in both group and individual sessions. For example, a group insulin start program *(38)* resulted in greater treatment satisfaction and similar glycemic control when compared to an individual program. Little research on the cost effectiveness of group education exists, yet is often is cited as the justification for group DSME programs.

In an attempt to gain further insight into the optimal format and length for education, Campbell et al *(39)* conducted a randomized trial comparing 4 conditions: a basic 2-session program, an individual 12-session program, a 3-d group education program, and an individualized behavioral program. Participation in any of the 4 programs was associated with improvements in A1C and body mass index (BMI), with no significant differences among the conditions.

The majority of DSME studies have evaluated either individual or group education programs, often provided by a diabetes nurse educator and/or dietitian. Very few studies have examined who provided the education to elucidate which health care team members are most effective and most cost-effective. One meta-analysis provided data that educational interventions led by physicians had slightly better outcomes than those led by other health professionals, however it was not clear if the impact was owing to education or owing to other inventions (e.g., medications, insulin doses adjustments) *(30)*. Patients participating in either nurse or dietitian-led programs had similar outcomes *(30)*.

Although the majority of studies have been conducted using structured DSME interventions, DSME also occurs informally. Gillard et al *(40)* reported a positive impact on A1C levels and SMBG behavior by providing informal education as part of a retinopathy screening program. The educational intervention included:

- Providing DSME materials in waiting areas
- Education during the screening examination specific to that patient's findings
- Reviewing test results individually with patients, answering questions about those results and offering options for behaviors that would affect the results.
- Having a diabetes educator available in the waiting area to answer questions for patients and their families while they were.

DSME also occurs during provider visits. Although less is known about DSME in this context, numerous studies have demonstrated that patients remember less than 50% of what was said during the medical visit, and patients with low functional health literacy may remember even less *(41)*. Functional health literacy is defined as a measure of a patient's ability to perform basic reading and numerical tasks required to function in the health care environment and is distinct from education level and language ability *(42)*. Low functional health literacy has been associated with poorer glycemic control among people with diabetes *(43)*.

An effective strategy to improve the effectiveness of provider communication for self-management is the "ask, tell, ask" or interactive communication loop *(44)*. The interaction begins with the provider asking the patient what concerns or questions they have about their diabetes, information or support is then provided based on the patient's issue, and the patient is then asked to repeat or "teach back" the information. The interaction continues with the provider asking if there is additional information needed. This patient-centered communication strategy not only checks for recall, but can also uncover health beliefs, provide the opportunity to reinforce and tailor health messages and open a dialog with patients *(45)*. A recent study *(41)* showed that glycemic control was independently associated with physician's application of this interactive communication strategy.

There is also evidence that patients who are aware of their A1C level and target levels, are more likely to achieve those targets *(46)*. A greater understanding of the treatment, greater belief in the efficacy of the treatment and shared decision-making increase the likelihood of agreement between patients and providers on goals or strategies. Greater agreement is associated with self-efficacy and self-reported self-management behaviors *(46)*.

## INFLUENCING DIABETES SELF-MANAGEMENT THROUGH PATIENT EMPOWERMENT

Self-management requires considerable effort that must be sustained over a lifetime of diabetes. Patients are frequently asked to make multiple changes in their lives and lifestyle, learn new skills and make multiple decisions that can have both short and long-term consequences. At the same time, patients are also dealing with the emotional consequences of a chronic illness that can result in multiple complications and premature death. The use of new technologies and a greater emphasis on "treating to target" increase both the degree of freedom and the level of responsibility patients must assume for their diabetes. Although it is tempting to try to "motivate" patients through use of positive or negative reinforcement (e.g., praise, criticism, scare tactics) the degree of motivation required to implement and maintain behavior changes in diabetes is most effective when it is internally generated and directed at behaviors that are meaningful to that individual *(47)*.

There has been a shift from didactic education to programs that are more theoretically and empowerment based *(25,26,28,31)*. Self-determination theory predicts that when patients have autonomy, are helped to identify what is important to them and set goals, then they are more internally motivated to care for their diabetes than when they are feeling controlled or pressured. Traditional, compliance based approaches where health professionals expected patients to follow a diet, exercise and medication regimen created by the health professional were frequently viewed by patients as an encroachment on their personal autonomy. Based on the attention given to noncompliance, it is clear that most adults resisted this approach, and often asserted their autonomy by choosing not to implement the recommendations. In addition, psychosocial and other concerns are rarely addressed in this approach.

In a recent study *(48)* Certified Diabetes Educators (CDE) were asked to indicate which theoretical approaches (respondents were allowed to endorse more than one approach) had most influenced the way they provide DSME. The approach most frequently chosen (98%) was empowerment. Empowerment in this context is defined as helping patients discover and use their own innate ability to gain mastery over their diabetes *(49)*. The empowerment approach to DSME seeks to provide information, resources, and psychological and social support to patients so that they can make informed, personally meaningful and realistic self-management decisions *(49)*.

An empowerment based education program is patient-centered rather than content-driven and provides patients with the knowledge and skills they need to make informed choices *(49–51)*. In addition, patients are facilitated to identify and achieve their own goals rather than those chosen by health care professionals. This approach acknowledges the expertise of patients in knowing their own values and abilities. Within the empowerment framework, diabetes self-management education is designed to meet the needs identified by and with the individual or group of patients so that they can become informed, active participants in their own care. This approach has been effective when empowerment strategies are taught separately *(50)* or as part of a comprehensive education program *(52,53)*.

Two recent studies have evaluated the efficacy of an empowerment-based, DSME intervention in which clinical and psychosocial concerns were addressed in an integrated fashion *(52,53)*. These studies evaluated a program consisting of 6 weekly group sessions (90-min in length) with follow-up for 1 yr as well as a program held weekly for 6 mo. In the latter program, patients were encouraged to attend the weekly group sessions only when they felt they needed support. The design and conduct of the group sessions in both programs was essentially the same. Lectures were completely eliminated and the curriculum consisted of the concerns, problems and questions introduced by the participants. The clinical and psychosocial aspects of living with diabetes were not separated. The program emphasized a patient-centered approach supportive of and responsive to patient-specific needs, lifestyle and goals. The CDEs who led the program helped patients identify personally relevant and meaningful issues, answered their questions and endeavored to ensure that the patients' self-management goals and plans truly reflected their concerns. The initial program resulted in significant differences in A1C, serum cholesterol, HDL, weight, blood glucose monitoring, perceived understanding and attitude about diabetes. These differences were sustained or improved after 1 yr. Key components of this program included:

- Reflecting on relevant experiences
- Discussing the role of emotion
- Engaging in systematic self-directed goal-setting and problem-solving
- Answering clinical questions

One of the most effective interventions to promote behavioral change is the use of self-directed goal setting *(50,52–56)*. Goal-setting is a process that results in an action plan, which is usually a concrete, measurable, short-term goal *(55)*. Table 3 outlines a five-step process for goal-setting that supports a collaborative approach, addresses both behavioral and psychosocial issues and is consistent with empowerment, self-motivation and readiness to change *(57)*.

The model of readiness to change that is most relevant for influencing self-management comes from the motivational interviewing (MI) model *(44,55)*. In this approach, readiness equals importance plus confidence

**Table 3**
**5-Step goal setting model**

| |
|---|
| Identify the problem |
| *What is the most difficult or frustrating part of caring for your diabetes at this time?* |
| Determine feelings and their influence on behavior |
| *How do you feel about this issue? How are your feelings influencing your behavior?* |
| *On a scale of 1 – 10, how important is it for you to address this problem? On a scale of 1 – 10, how confident do you feel that you can resolve this issue?* |
| Set a long-term goal |
| *What do you want? What do you need to do? What problems to you expect to encounter? What support do you have to overcome these problems? Are you willing/able to take action to address this problem?* |
| Make a plan for a behavioral step |
| *What will you do this week to get started working toward your goal?* |
| Assess how the experiment worked |
| *How did it work? What did you learn? What might you do differently next time?* |

Adapted from Funnell 2004; Clinical Diabetes *(57)*

**Table 4**
**AADE 7 key self-care behaviors**

| |
|---|
| • Healthy Eating |
| • Being Active |
| • Monitoring |
| • Taking Medication |
| • Problem Solving |
| • Healthy Coping |
| • Reducing Risks |

Adapted from Mulcahy, 2003; The Diabetes Educator *(58)*

or self-efficacy, rather than assigning a particular readiness stage *(55)*. This approach is more relevant for an illness such as diabetes where there are numerous behaviors patients can choose to implement. Asking the patient to identify a problem area they wish to address and then asking the patients to rate on a scale of 1–10 how important it is to them and how confident they are they can to address this issue, guides the provider in providing appropriate interventions to increase the patients' knowledge, skills or confidence, and guides patients in their selection of a long-term goal and behavioral strategy. Self-evaluation is a critical component of this process that is often neglected. Patients are encouraged to think of their short-term goals as a series of behavioral experiments. Experiments provide information and feedback regardless of their success or failure *(52,57)*. Therefore, the critical question for providers to ask on follow-up, is not were you successful, but what did you learn and what will do or not do differently next time.

Goal-setting is effective because it creates a useful way to implement several of the behavioral theories described above. Patients identify the issue or problem as one they are ready to address. They are encouraged to consider their emotional response to this issue in developing their plan. Their self-efficacy or confidence in their ability to change is identified and enhanced through success in a series of progressive steps towards a long-term goal. The action plan identifies their intention or commitment to make the change they have identified.

A literature review of the available evidence by Mulcahey et al *(58)* forms the basis for the identification of 7 key patient behaviors known as the AADE 7. These behaviors are used to identify, document and evaluate the effectiveness of DSME and the goal-setting process for individual patients and to measure aggregate outcomes of the self-management process (see Table 4).

Although diabetes self-management education (DSME) is the essential first step for patients to become effective self-managers, providing on-going diabetes self-management support (DSMS) is the equally necessary second step if these efforts are to be sustained. The purpose of DSME is to help patients make informed decisions, to evaluate the costs and benefits of those choices and overcome barriers. The purpose of DSMS is to provide the support patients need to sustain their self-management efforts *(57)*.

## INFLUENCING DIABETES SELF-MANAGEMENT THROUGH ON-GOING SUPPORT

Because diabetes is a chronic illness, it is unrealistic to expect that a one-time educational intervention is adequate. Patients need on-going education and self-management support. Although the initial, comprehensive education may best be done outside the practice setting, the office setting is ideal for on-going education and self-directed goal-setting for behavior change *(4,54,55,59)*.

The purpose of on-going diabetes self-management support (DSMS) is to assist patients to initiate and sustain behavioral changes, address barriers, concerns and psychosocial issues, be screened for depression or anxiety and continue to learn about diabetes and new treatments as needed. The goal is to facilitate patients self-care and behavior change efforts so that they can become effective daily managers of their diabetes. *(53,57)* Most DSME intervention studies are based on a one-time event that provides the fundamental information patients need to begin to manage their diabetes. However in studies where longer-term outcomes are measured, the results achieved generally begin to decline after about 6 mo without continued contact *(27)*. Based on her 2 meta-analyses, Norris concluded that regular reinforcement is more effective than one-time education *(31)*.

The need for on-going DSMS is particularly important in the behavioral and psychosocial domains. At the conclusion of the empowerment-based program described earlier, patients were given the option of phone calls from a nurse to set behavioral goals or a monthly support group that included goal-setting facilitated by a nurse and dietitian. Through this extended contact, postprogram metabolic improvements were sustained or improved equally in both groups *(52)*.

Findings from the DAWN study *(60,61)* reinforced our understanding of the burden of diabetes. In this study, telephone or face-to-face interviews were conducted with over 5,000 patients, 2,700 physicians and 1,100 nurses. Over half of the patients surveyed reported feeling stressed or anxious about their diabetes. They further indicated that they received very little in the way of psychosocial support from their care providers, and would like to receive more. The majority of health professional participants recognized that psychosocial issues played a large part in behavioral problems, yet most did not feel equipped to address these needs. The results of the DAWN study showed very clearly that people with diabetes find their illness distressing and difficult, even when they are able to effectively manage the metabolic and other self-care aspects *(60,61)*.

Patients frequently provide clues or bring up issues related to their level of distress, however this does not appear to be adequate to ensure that they are addressed. Audiotapes of physician/patient interactions reviewed by Levinson et al *(62)* showed that primary care providers responded only 21% of the time when patients raised issues related to psychological or social concerns. Repeating the concerns several times during the visit did not increase the likelihood they would be addressed. Surprisingly, missing opportunities to respond to these issues tended to lengthen, rather than shorter the visit *(62)*.

## INFLUENCING SELF-MANAGEMENT: COLLABORATIVE CARE

Empowerment-based diabetes care, DSME and DSMS require a collaborative approach in which health care professionals are responsible **to** patients rather than **for** them *(63)*. The collaborative approach to diabetes care is based on the recognition that diabetes and its self-management essentially belong to the patient. Therefore, to be effective, a diabetes plan must be developed collaboratively and be consistent with the patient's needs, resources and goals *(63)*.

There is a great deal of evidence that a collaborative approach improves patient outcomes *(55)*. A comprehensive review concluded that a participatory relationship between patient and provider is one of the most successful factors in promoting self-management behaviors *(64)*. In a randomized control trial, patients who were provided with a 20-min intervention to increase their participation in decision-making and information seeking, showed significant decreases in A1C values, compared with a control group that received only didactic information *(45)*. The level of knowledge for both groups was the same.

Patients in the DAWN study who perceived a positive relationship with their providers reported better self-management behaviors, less diabetes–related distress and better metabolic outcomes *(60,61)*. Provider/patient interactions that promote assertive communication and collaboration have been shown to result in improved health related behaviors, metabolic control and functional status, more positive self-evaluation of health, and greater patient satisfaction *(44,65,66)*. Heisler et al *(67)* found significant associations among improved information giving by the physician, more participatory decision-making, enhanced self-efficacy, healthier behavior and better outcomes *(67)*.

A model that has been proposed as a way for providers to conceptualize increased collaboration with individual patients is the 5As model. *(4)* This model can also help the clinician provide and evaluate different components of the interaction. The 5 A's are:

- Assess: Beliefs, behavior and knowledge.
- Advise: Provide specific information about health risks and benefits of change.
- Agree: Collaboratively set goals based on patient's interest and confidence.
- Assist: Identify personal barriers, strategies, problem solving and social-environmental support.
- Arrange: Specify plans for follow-up and refer to community and other resources.

All of these steps may not be possible during each office visit, and can appropriately be the role of other professional staff members *(4)*. In addition, providers can begin each visit by asking patients what concerns they need addressed today, and end by asking what they plan to work on between this visit and the next.

One of the dilemmas for most providers is that our current health care systems are not designed to provide (nor do they reimburse) the type of collaborative care and DSMS the evidence indicates is needed. Technology can be used as an adjunct to health professional interaction *(68,69)*, but still requires professional involvement.

The Chronic Care Model has been proposed as an effective model to establish systems that support and sustain the efforts of patients and health professionals to achieve recommended diabetes outcomes. In this model, the informed, empowered patient works with a proactive health care team and is linked to community and other DSME and DSMS resources *(65,70)*.

Health care teams can effectively provide much of the DSMS patients need *(4,54,61,71,72)*. Strategies that increase the effectiveness of teams include:

- Referring patients for diabetes self-management education.
- Incorporating ongoing patient-centered education, goal-setting and collaboration into every-day care.
- Identifying key staff (e.g., nurse educators), but recognize that all staff are responsible for supporting self-management.
- Communicating role in self-management to patients.
- Enhancing the role of the nurse.
- Instituting computerized tracking systems.
- Regularly recalling and reviewing patients or providing follow-up by nurses.
- Implementing patient-centered interventions (DSME; encouraging patients to identify problems and solutions).
- Implementing on-going follow-up and DSMS.

Many of these strategies can be incorporated into practical interventions, often coordinated by case-mangers or in nurse-led clinics *(71–79)*. In a recent study, nurse case managers were effective for improving outcomes when their role included blood glucose management and goal-setting *(78)*. More time with the nurse resulted in greater improvement. A recent review of diabetes disease management programs *(79)* showed that they can significantly

**Table 5**
**Evidence for Diabetes Self-management Education (DSME) and Diabetes Self-management Support (DSMS)**

| |
|---|
| • DSME is effective for type 2 diabetes, especially in the short-term. **(1A)** |
| • Traditional knowledge based DSME is essential but not sufficient for sustained behavior change. **(1A)** |
| • No single strategy or programmatic focus shows any clear advantage, but interventions that incorporate behavioral and affective components are more effective. **(1A)** |
| • DSME has evolved from primary didactic interventions into more theoretically based empowerment models. **(1B)** |
| • Theoretically based empowerment models of self-management education and support are effective for influencing outcomes. **(1B)** |
| • Effective DSME is tailored to the patient's preferences, social and cultural situation. **(1B)** |
| • DSME is most effective when coupled with appropriate care and reinforcement by all health care professionals. **(1C)** |
| • Regular reinforcement of DSME is more effective than a one-time intervention for influencing outcomes. **(1B)** |
| • Low functional health literacy is associated with poorer glycemic control. **(1A)** |
| • Interactive communication strategies by physicians are associated with improved outcomes. **(1B)** |
| • Improved relationships with providers result in improved outcomes. **(1C)** |
| • Self-directed goal setting is an effective strategy for behavior change in diabetes. **(1A)** |
| • Patients are anxious and distressed about diabetes, and want more help from their providers than they currently receive. **(1C)** |
| • Psychosocial issues influence self-management behaviors. **(1C)** |
| • Health care teams can effectively provide DSMS. **(1B)** |
| • Case-management is an effective strategy for influencing outcomes. **(1B)** |
| • Disease management is an effective strategy for influencing outcomes. **(1B)** |
| • Collaborative care improves patient outcomes. **(1B)** |

lower A1C levels by a 0.5% percentage point and increase screening for retinopathy and foot complications. When appropriately trained, peers can also successfully provide behavioral support *(56)*, either in person or using interactive voice technology systems *(80)*.

## CONCLUSION

Although we have answers to some questions as summarized in Table 5, there is still a great deal of work to do in the area of diabetes self-management, especially in terms of implementation. Two issues in particular stand out. Although we have known for some time that traditional, provider centered approaches for influencing diabetes self-management are not effective, making the shift to empowerment-based, collaborative models has been slow among providers, although it is occurring among certified diabetes educators. Progress has also been slow in the redesign of practices and health systems to incorporate collaborative models of care and more effectively use all of the members of the health care team to facilitate self-management.

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