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THEMED REVIEW

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Lifestyle Interventions and the Prevention and Treatment of Type 2 Diabetes

Abstract: *The diabetes epidemic is fueled by a societal increase in insulin resistance, caused by lifestyle factors, particularly excessive caloric intake and physical inactivity. Aging also plays a role in the increase in insulin resistance; however, even in older populations, the increase in insulin resistance appears to be attributable mainly to age-related obesity and inactivity. Insulin resistance reflects deposition of visceral, hepatic, and intramyocellular fat, while toxic messages from the adipose organ (free fatty acids, cytokines, and oxidative stress) impair insulin action to restrain glucose production in the liver and promote glucose disposal in muscle. Unexercised muscle is also insulin resistant because of intracellular sequestration of glucose transporters. These processes lead to hyperglycemia if compensatory secretion of insulin is inadequate due to decreases in pancreatic β-cell function and mass, ultimately resulting in the development of prediabetes and, later, type 2 diabetes mellitus (T2DM). Lifestyle interventions, programs that promote diabetes risk reduction and weight loss through behavior change, increased physical activity, and dietary modification, can decrease insulin resistance and prevent or delay the development of prediabetes and progression to T2DM. Lifestyle interventions are also important to improve diabetes management, particularly early in the natural history before loss of β-cell function and mass is so extensive that multidrug pharmacologic therapy is required. Effective interventions often include both an increase in physical activity (ideally, at least 150 minutes per week of moderate-to-vigorous aerobic exercise and strength training) and dietary modification to promote weight loss.*

> ...there is strong evidence that lifestyle interventions . . . can prevent or delay the development of T2DM in high-risk populations.

Keywords: type 2 diabetes mellitus; prediabetes; lifestyle; prevention

Glucose intolerance, in the form of type 2 diabetes mellitus (T2DM) or prediabetes, a precursor to the development of T2DM, is a major public health problem. T2DM is an economically costly disease[1] and is a major contributor to morbidity and mortality. T2DM can lead to renal dysfunction, peripheral and autonomic neuropathy, vision problems, and cardiovascular disease.[2] In the United States alone, from 2005 to 2050, the prevalence of diagnosed diabetes is expected to more than double from 5.6% to 12.0%.[3] In 2005 to 2006, the prevalence of prediabetes and diabetes combined was estimated to be 42.3% for Americans aged 20 years or older. The total prevalence of diabetes (diagnosed and undiagnosed) was estimated to be 12.9%, approximately 40% of which was undiagnosed.[4] Worldwide, the number of adults aged 20 to 79 years with diabetes is estimated to be 246 million (prevalence = 6.0%), and the number of people with impaired glucose tolerance is 308 million (prevalence = 7.5%).[5]

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Fortunately, there is strong evidence that lifestyle interventions, programs promoting behavior change to improve diet, increase physical activity, and reduce weight, can prevent or delay the development of T2DM in high-risk populations and that these programs also result in better management and improved outcomes for patients with T2DM. This review describes how lifestyle choices affect insulin action, examines the effects of lifestyle interventions on prediabetes and T2DM, and provides recommendations for physicians and other health practitioners looking to promote lifestyle change among their patients who have these conditions or are at risk of developing these conditions.

The Scope of Glucose Intolerance

Glucose intolerance ranges from prediabetes to diabetes. Prediabetes, a precursor to and risk factor for diabetes, includes the following conditions: impaired fasting glucose (IFG), a fasting plasma glucose (FPG) of 100 to 125 mg/dL following the American Diabetes Association definition used in the United States or 110 to 125 mg/dL following the World Health Organization definition used elsewhere; or impaired glucose tolerance (IGT), in a 75-g oral glucose tolerance test (OGTT), a 2-hour postload glucose of 140 to 199 mg/dL when diabetes is not present. Diabetes is defined as FPG >125 mg/dL, 2-hour postload glucose >199 mg/dL, or both. Measurement of hemoglobin A1c is a less accurate and relatively insensitive approach to assessment of glucose intolerance.[6] Approximately 95% of all cases of diabetes are T2DM. Glucose intolerance is a global problem, affecting a large percentage of the population in both the United States and abroad. Furthermore, the often-asymptomatic nature of diabetes complicates efforts to estimate the true prevalence of the disease. Without symptoms, many people with diabetes fail to be identified until much later in their disease course, when secondary complications have developed; screening on the basis of T2DM risk factors such as older age, overweight, minority race/ethnicity, or the metabolic syndrome can permit earlier diagnosis, but random plasma glucose levels appear to constitute a better—and less expensive—screening tool.[7-9]

Glucose Intolerance in the United States

For the adult US population (aged 20 years or older), it is estimated that 12.9% of the population has diabetes, of which approximately 40% is undiagnosed (prevalence of diagnosed diabetes = 7.7%; prevalence of undiagnosed diabetes = 5.1%).[4] The prevalence of diagnosed and undiagnosed diabetes increases with age among Americans, with the total diabetes prevalence peaking among 60- to 74-year-olds (30%). The proportion of diabetes cases that are undiagnosed ranges from 32.5% for 20- to 39-year-olds to 46.0% for individuals 75 years of age or older.[4] Although women have a slightly higher prevalence of diabetes than men (13.3% vs 12.4%, respectively, for people aged ≥20 years), a greater percentage of total diabetes in men is undiagnosed (42% vs 37.9% in women). Diabetes prevalence is expected to rise, with the prevalence of diagnosed diabetes expected to reach 12% by 2050.[3]

Furthermore, the burden of diabetes across racial groups in the United States is unequal. Among Americans aged 20 years or older, the prevalence of diabetes is 17% for non-Hispanic blacks, 14.7% for Mexican Americans, and 12.2% for non-Hispanic whites. Although non-Hispanic blacks have the highest diabetes prevalence, they have significantly less undiagnosed diabetes; the percentage of total diabetes that is undiagnosed in non-Hispanic blacks is 24.2%, while more than 40% of total diabetes is undiagnosed in Mexican Americans and non-Hispanic whites.[4] Native Americans and Asian Indians have also been reported to have high rates of diabetes; in one study of Asian Indians living in a major US city, the reported prevalence of diabetes was 18%.[10]

The prevalence of prediabetes is even greater. Among US adults aged ≥20 years, the prevalence of prediabetes is 29.5%. IFG is more common than IGT; the prevalence of IFG is 25.7% (using FPG 100-125 mg/dL), compared with 13.8% for IGT. Men represent a greater proportion of individuals with IFG (32.1% vs 19.8% for women). IGT prevalence does not vary significantly by sex. Among race-ethic groups, prediabetes prevalence ranges from 25.1% for non-Hispanic blacks to 31.7% for Mexican Americans.[4]

The Global Burden of Glucose Intolerance

Estimates place the worldwide prevalence of diabetes for all age groups at 2.8%, with an expected rise to 4.4% by 2030.[11] The number of adults aged 20 to 79 years with diabetes is estimated to be 246 million (prevalence = 6.0%),[5] and this number is expected to rise.[12] Although diabetes is found in all populations throughout the world, 3 countries share the bulk of the diabetes burden: the United States, India, and China had more than 70 million people with diabetes in 2000, an estimate projected to increase to nearly 152 million by 2030. Importantly, these projections assume a static obesity prevalence, which is unlikely given the overall population trends of increasing weight, aging, and urbanization.[11]

Traditionally, T2DM has been thought of as a disease of affluence. This is no longer the case; T2DM incidence and prevalence are increasing at alarming rates in rural and aboriginal communities.[13-15] For example, in India, a country where 70% of the population lives in rural communities, there are more than 40 million cases of T2DM, the highest number of diabetes cases worldwide.[5,16] In 2005-2006, a study in Sri Lanka reported that the prevalence of diabetes for adults aged 20 years or older in rural communities was 11.0%, while in urban settings, the prevalence of diabetes in adults was 13.6%.[17] In China, there are almost 40 million cases of diabetes, almost equally divided between those living in rural and urban communities.[5]

Global estimates of the size of the undiagnosed diabetes population vary

Table 1.

Both Genetics and Environment Affect Risk of Type 2 Diabetes[a]

	Pima U.S.	Pima Mexico	Other Mexicans
Diabetes prevalence	37.5%	8.0%	2.5%
Obesity	69.3%	13.2%	17.7%
Physical Activity	7.6 h/wk	27.4 h/wk	27.1 h/wk

[a] Adapted from Schultz et al,[26] *Diabetes Care.* 2006;29:1866.

by region studied. A 2003 analysis of 11 Asian cohorts, including Chinese, Japanese, and Asian Indian populations, found that undiagnosed diabetes prevalence ranged from 1.0% to 6.5% across all age groups among Chinese and Japanese people and from 1.9% to 7.2% among Asian Indians.[18] In Korea, it was estimated that in 2001, 2.6 million adults had diabetes, 43% of whom were undiagnosed.[19] A 2003 Danish study found that among people with diabetes aged 45 years, 82% of the men and 70% of the women were previously undiagnosed; among people aged 60 years, the proportions were 63% and 52%, respectively. In this population, men were significantly more likely to be undiagnosed compared with women.[20] Another study comparing 13 European cohorts found undiagnosed diabetes rates to be highest for men in the youngest age ranges (30-39 and 40-49 years; 70% and 60% of patients previously undiagnosed, respectively), with the rates of undiagnosed diabetes decreasing with increasing age; in women, the highest proportion of undiagnosed diabetes was for individuals aged 40 to 49 years (58%), although there was no clear trend of increasing or decreasing prevalence over time.[21] Across all age ranges, undiagnosed diabetes (by FPG, postload glucose, or both) was between 0% and 4.0% for men and 0% to 9.2% in women. The prevalence of diabetes in Australians aged >25 years was 8.0% in men and 6.8% in women based on national survey data from 1999 to 2000. Approximately half of all people with diabetes in Australia were previously undiagnosed.[22]

Although data are scarce, particularly for IFG, the global prevalence of prediabetes has been described in recent studies. Across Europe, the prevalence of prediabetes rose with age: across all studies, the prevalence was <15% for individuals aged 30 to 59 years and between 15% and 30% for those 60 years and older. Unlike in the United States, where the prevalence of IGT did not differ significantly between men and women,[4] IGT was more prevalent in women than in men in all age groups, ranging from 4.5% in the youngest age group to 24.6% in the group aged 80 to 89 years. The rates of IFG were consistently lower in women compared with men (range, 3.2%-10.1% in men and 2.6%-5.9% in women) when compared by age group. Prediabetes by any definition was most common in men aged 40 to 69 years.[21] Similarly, in the Danish population, IGT was more frequent in women aged 30 to 35 years than in men in the same age group (9.9% vs 5.8%). For IFG, the reverse was true: men were significantly more likely to have IFG ($P < .0001$). In both sexes, impaired glucose regulation rose with increasing age.[20] For Asian populations, prediabetes prevalence was <18% for individuals aged 30 to 59 years and 18% to 26% for those 60 years or older in Chinese and Japanese populations and <24% for Asian Indians aged 30 to 59 years and 20% to 27% for Asian Indians 60 years of age or older.[18] The Korean prevalence of prediabetes by IFG criteria was 23.9%, or roughly 8.1 million people.[19]

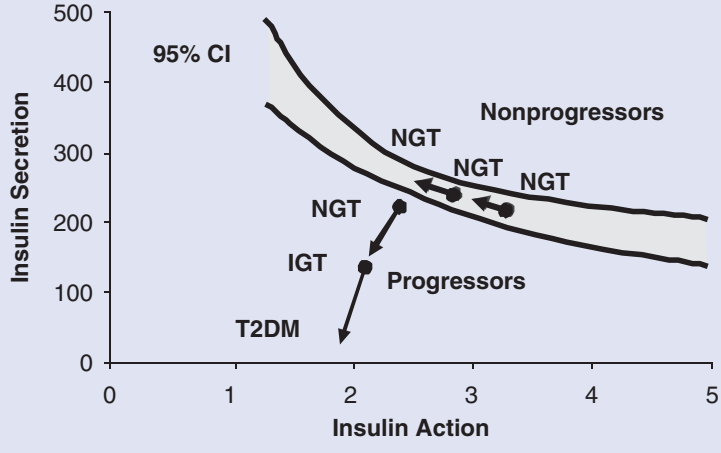
The Rising Prevalence of Diabetes and Prediabetes Is a Result of Lifestyle Factors

The diabetes epidemic is fueled by a societal increase in insulin resistance, caused by secular increases in underlying lifestyle abnormalities—excessive caloric intake and physical inactivity.[23] Both body mass index (BMI) and physical activity are independently and strongly associated with diabetes.[24] Aging is associated with increased insulin resistance as well; however, this appears to be attributable mainly to age-related obesity and inactivity, because older individuals who are nonobese and physically fit are not insulin resistant compared with nonobese, fit, younger individuals.[25]

Obesity and inactivity increase the risk of development of diabetes in genetically susceptible individuals. This interaction between genetics and the environment is well seen in the Pima Indians. Adult Pimas living on a reservation in Arizona have the highest prevalence of T2DM in the United States (37.5%; see Table 1); 69% are obese, and they average less than 8 hours per week of physical activity. In contrast, Pimas in Mexico, with the same genetic background but less obesity and much more physical activity, have an 8.0% prevalence of diabetes. Non-Pima Mexicans with comparable levels of obesity and physical activity have only a 2.5% prevalence of diabetes.[26] Thus, when obesity and physical activity are comparable (Mexican Pimas compared with other Mexicans), genetics increases the prevalence of diabetes roughly 3-fold, but within the same genetic group (Pimas in the United States compared with those in Mexico), the environment (obesity and inactivity) increases the prevalence of diabetes almost 5-fold. Similarly, a study of second-generation Japanese Americans in Seattle found the prevalence of diabetes (diagnosed and undiagnosed) to be approximately 20%, roughly 4-fold higher than the prevalence of diabetes among a similar population in Japan and twice as high as non-Hispanic whites in

Figure 1.

Glucose disposition analysis: why diabetes develops. Plot of insulin secretion versus insulin action in Pima Indian subjects who did or did not progress form normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM).The 95% Confidence Interval (95% CI) for the NGT curve is shown. Adapted from Weyer, et al.[44] *J Clin Invest.* 1999;104:787.



the United States at the time.[27] An earlier study of the same population found other changes associated with migration: Japanese Americans weighed more than their Japanese counterparts, although this was not statistically significant, and Japanese Americans derived a statistically significantly greater percentage of daily calories from animal protein as compared with similarly aged men from Japan.[28] In the same way, the increasing global prevalence of diabetes reflects both genetics (an expansion of nonwhite populations who have a predisposition to develop diabetes) and the environment (an increase in age, along with a lifestyle-related increase in overweight and sedentary activity).

Moreover, in genetically at-risk populations such as South Asians, the prevalence of T2DM risk factors, such as insulin resistance, increased fat mass, and central obesity, is high,[29-33] even with only modest increases in BMI. Asian Indians and other South Asians have higher rates of T2DM[34-36] and develop T2DM at younger ages[37,38] and at lower BMIs[38,39] compared with whites. Similarly, in Singapore Chinese, BMIs of 18.5 to 23 kg/m^2 were associated with a 2.5-fold increased risk of diabetes compared with BMIs <18.5 kg/m^2.[40]

How Lifestyle Factors Cause the Development of Prediabetes and Diabetes

Obesity and inactivity increase insulin resistance via 2 mechanisms: (1) nonphysiologic deposition of fat in visceral, hepatic, and intramyocellular sites, and (2) intracellular sequestration of GLUT4 glucose transporters in unexercised muscle, resulting in reduced glucose uptake.[41] Interestingly, exercise alone may not attenuate insulin resistance if sedentary activity is excessive; time spent being sedentary is predictive of high fasting insulin levels, regardless of the time spent doing moderate-to-vigorous intensity activities, independent of age, sex, fat mass, fasting insulin, smoking status, and follow-up time.[26] The excess fatty acids interfere with insulin receptor signaling and lead to decreased glucose transport, often referred to as lipotoxicity, and activate protein kinase C through increased fatty Acyl-CoA and diacylglycercols. Free fatty acids, produced more readily in the visceral abdominal fat, may decrease insulin sensitivity, impair vascular reactivity, and also increase endothelial dysfunction.

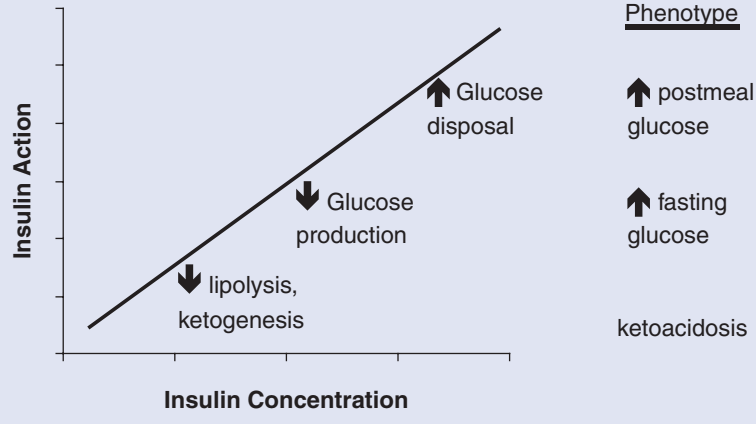
The nonphysiologic deposition of fat appears to be a major contributor to insulin resistance, and visceral and especially intrahepatic fat are particularly associated with insulin resistance.[42] Toxic messages from the adipose organ such as free fatty acids, cytokines (eg, an increase in tumor necrosis factor-α and a decrease in adiponectin), and oxidative stress, impair insulin action to restrain glucose production in the liver and promote glucose disposal in muscle.[43]

These processes of insulin resistance lead to hyperglycemia if compensatory secretion of insulin is inadequate, potentially resulting in prediabetes, then T2DM. Why diabetes develops is illustrated in Figure 1. Normal glucose tolerance is a function of both insulin secretion and insulin action. Across a range of insulin action, glucose homeostasis can be maintained if insulin secretion is adequate. If insulin action falls (eg, insulin resistance increases due to weight gain and/or inactivity) but insulin secretion increases, normal glucose tolerance (NGT in Figure 1) is sustained and progression to diabetes does not occur. However, if insulin secretion cannot increase to compensate for the insulin resistance, then patients progress to prediabetes (IGT in Figure 1) and, if this continues over time, may develop T2DM. Abnormalities of insulin secretion in persons with frank diabetes include reduced or absent first-phase responses to intravenous glucose,[45] delayed and blunted secretory responses to ingestion of a mixed meal,[46] alterations in the patterns of insulin secretion,[47] and increases in the plasma concentrations of proinsulin relative to those of insulin.[48]

The development of hyperglycemia (inadequate β-cell compensation for insulin resistance) reflects both impaired pancreatic β-cell function and loss of β-cell mass. The loss of β-cell mass is due to apoptosis, and β-cell mass is about 60% of normal in individuals with prediabetes and 40% of normal in individuals with diabetes.[49] Accordingly, the extent to which lifestyle change to

Figure 2.

Degree of insulin deficit explains clinical phenotype. Shown schematically are (a) the relative progression of insulin concentrations required for different actions of insulin (to decrease lipolysis and ketogenesis, to decrease hepatic glucose production, and to increase peripheral glucose disposal) along with (b) the clinical phenotypes corresponding to insulin concentrations insufficient for that aspect of insulin action (diabetic ketoacidosis, elevated fasting glucose, and elevated postprandial glucose).



reduce insulin resistance can restore normoglycemia in individuals with prediabetes or diabetes depends on the β-cell defect, which is reflected by the clinical phenotype. As shown schematically in Figure 2, the highest insulin concentrations are required to promote glucose disposal into fat and muscle, the next highest to restrain glucose production in the liver, and the lowest to restrain lipolysis and ketogenesis. Thus, a mild β-cell defect presents as postprandial hyperglycemia, a moderate defect as fasting hyperglycemia, and a severe defect as ketoacidosis.

If the β-cell defect is mild, as in patients with prediabetes, lifestyle change to reduce insulin resistance can often restore normoglycemia and help prevent progression to diabetes. But if the β-cell defect is more severe, as in patients who are later in their natural histories and exhibit marked fasting hyperglycemia, lifestyle change is important to help control glucose excursions but may not restore normoglycemia, and pharmacologic therapy will be needed. Lifestyle change also tends to improve postprandial hyperglycemia more than fasting hyperglycemia, because exercise can reduce insulin resistance in muscle (the major target of glucose disposal) but has less effect on the liver (the source of glucose production).

Different categories of prediabetes carry different risks of progression to frank diabetes. The overall risk for progression to T2DM for people with prediabetes is between 25% and 40% over 3 to 8 years.[50-52] However, patients with isolated IFG and patients with isolated IGT have different risks of progression, and patients with both abnormalities have a generally higher risk of progression than individuals with either abnormality alone. A 2004 study demonstrated that people with IGT are more insulin resistant than people with IFG and that IGT is more strongly associated with increases in cardiovascular disease[53]—an important distinction because IGT can be identified only through an OGTT, a test that is currently underutilized in the United States. Even within the category of IFG, people with FPG levels of 100 to 109 mg/dL have been shown to be at less risk of progression to diabetes than people with FPG levels of 110 to 125 mg/dL, likely because patients in the former category are earlier in their natural histories.[54] As noted above, measurement of hemoglobin A1c is a less accurate way to identify glucose intolerance.

Thus, the development of glucose intolerance depends on both the degree of insulin resistance and the extent of β-cell reserve. Everyone who develops insulin resistance will not develop prediabetes, and everyone who develops prediabetes will not develop T2DM. However, because of the rising rates of obesity and sedentary activity and the resulting increase in insulin resistance, it is essential to emphasize healthy lifestyles to reduce insulin resistance and limit the development of glucose intolerance in individuals who are at risk, in order to minimize the effects of these conditions on the health of individuals and society. Furthermore, as glucose levels increase over the natural history of T2DM (insulin resistance to prediabetes to T2DM), β-cell mass and function decrease, making it harder for the body to sustain normal glucose. Accordingly, it is particularly important to use lifestyle change to buy quality life-years of normoglycemia early in the natural history of T2DM, via decreased insulin resistance and reduced β-cell challenge, since lifestyle change is less likely to restore normoglycemia later in the natural history.

Lifestyle Interventions for Diabetes Prevention

Lifestyle interventions are programs that address the total lifestyle of an individual with the goals of decreasing excess weight, increasing physical activity, and improving the quality of the diet. Five large trials, 4 of which were randomized, showed that lifestyle interventions decrease T2DM incidence in people with prediabetes.[52,55-58] A meta-analysis of randomized controlled trials of lifestyle interventions for T2DM prevention found that compared with control or placebo groups, lifestyle intervention participants had a 0.84 mmol/L decrease in 2-hour plasma glucose (95% confidence interval, 0.39-1.29) and a 50% decrease in the 1-year incidence of T2DM (relative risk [RR], 0.55; 95% confidence interval, 0.44-0.69).[59] It is important to note that lifestyle interventions, by and large, have

had little effect on fasting glucose; only with extensive weight loss (for example, as a result of bariatric surgery[60]) is there an appreciable change in fasting glucose levels. Postload, 2-hour glucose reflects peripheral insulin resistance, while fasting glucose primarily reflects hepatic insulin resistance and a more severe β-cell defect (above).[61]

Two of these studies, the Finnish Diabetes Prevention Study (DPS) and the Diabetes Prevention Program (DPP) in the United States, showed a 58% reduction in diabetes incidence in study participants in the lifestyle group compared with those in the control group.[52,57] The DPS, a 5-center study conducted in Finland, randomized 522 middle-aged, overweight men and women with IGT to either usual care or an intensive lifestyle intervention. The DPS lifestyle intervention included 7 one-on-one consultations and between-visit phone calls with a nutritionist, as well as voluntary group sessions (eg, lectures, cooking classes, supermarket visits) in which the participant was taught about healthy food choices based on feedback from 3-day food records, goal setting, behavior change, and physical activity. In addition, participants were given the option of following a very low-calorie diet at months 6 to 7 to boost weight loss. The ultimate goals of the DPS were a ≥5% weight reduction, 30 minutes or more per day of moderate physical activity, a reduction in dietary fat (total fat <30% of total energy, saturated fat <10% total energy), and an increase in dietary fiber (≥15 g/1000 kcal).[57]

The DPP was similar to the DPS in several ways. The DPP was a multicenter, randomized trial of a lifestyle intervention for diabetes prevention with the goals of weight loss (≥7% of baseline weight) and increased physical activity (≥150 minutes per week). Diet change was not a primary goal of the lifestyle intervention; however, participants were counseled on dietary fat reduction as a tool for weight loss. The DPP study team randomized 3234 overweight men and women (aged 25 years or older) with IGT to a placebo arm, an intensive lifestyle intervention arm, or metformin (850 mg twice daily). A fourth trial arm, troglitazone, was discontinued because of potential liver toxicity of the drug. The DPP lifestyle intervention included 16 weekly sessions during the primary intervention period followed by 8 monthly maintenance sessions. Each individualized and culturally appropriate session was taught one-on-one with a case manager and covered topics including behavior change, goal setting, diet change (with a focus on fat reduction), and physical activity.[52,62]

The Da Qing Diabetes Prevention Study also used a multicenter, randomized design to study the effectiveness of lifestyle interventions for diabetes prevention in individuals with IGT. Participants were randomized by clinic to a standard-of-care control group or diet-only, exercise-only, or diet-plus-exercise education groups. Intervention participants were counseled individually by physicians about following a low-fat diet including personal calorie and food group intake goals and/or were taught to increase leisure-time physical activity by 1 to 2 units per day (units were defined as 30 minutes of mild-intensity exercise, 20 minutes of moderate-intensity exercise, 10 minutes of strenuous exercise, or 5 minutes of very strenuous exercise). Although the diabetes risk reduction in this study was not as great as that found in the DPP or DPS, the results are still impressive; compared with the control group, individuals in the diet, exercise, and diet-plus-exercise groups had reductions in diabetes incidence of 31%, 46%, and 42%, respectively. Furthermore, the lifestyle interventions were beneficial even to participants who were not overweight at baseline.[56]

Long-term follow-up shows that the effects of lifestyle interventions for reducing diabetes risk are reduced but remain highly statistically significant even when participants gain back some of the weight lost during the program.[52,56,57,63,64] The reduction in relative risk of diabetes in the DPS study after a median of 7 years of follow-up was 36%,[63] and after 20 years of follow-up in the Da Qing Diabetes Prevention Study, there was a 43% reduction in diabetes incidence in the combined lifestyle intervention groups compared with controls.[65] This decrease in effectiveness over time probably indicates that lifestyle interventions can only partially prevent or delay T2DM,[1] because the interventions affect insulin resistance but not β-cell function.[66] Over time, the ability of lifestyle change to decrease insulin resistance may be counteracted by an age-related increase in insulin resistance, allowing hyperglycemia to emerge because of the underlying β-cell defect. However, this does not detract from the importance of lifestyle change as a tool for improving the general health of the population and increasing an individual's disease-free, quality life-years.

The success of lifestyle interventions for different populations, comparing both within and between studies, shows that these programs are universally effective for diabetes prevention. Studies in the United States, India, Europe, and China all showed a reduction in diabetes risk.[52,55-57] In the DPP, which included men and women from different race and ethnic groups, age groups, and BMI levels, the lifestyle intervention was consistently effective at diabetes prevention.[52] It is important to note that lifestyle changes are effective tools for risk reduction, even in participants who are older and who have normal BMIs; in the DPP, the reduction in diabetes incidence for those in the lifestyle intervention compared with the placebo group was greater for those in the oldest age group (71% for individuals aged 60 or more years, compared with 48% for those aged 25-44 years) and for individuals with the lowest BMIs (65% for people with BMIs of 22 to <30 kg/m^2, compared with 51% for those with BMIs of ≥35 kg/m^2).[52] Peripheral insulin resistance increases with age, as reflected by higher 2-hour postload glucose values,[67] so lifestyle change would be expected to be more beneficial in the older group. The difference in effect based on BMI is probably attributable to the same percentage weight loss having less effect on insulin resistance for people with more body fat than for individuals with less baseline body fat.

Besides displaying a lower risk of T2DM, lifestyle intervention participants also have improved insulin responses,[68] whole-body insulin sensitivity,[69] markers of inflammation (C-reactive protein, interleukin-6,[70]

and plasminogen activator inhibitor[71]), aerobic capacity,[66] blood pressure, and plasma lipid levels.[72] Furthermore, the beneficial effects of lifestyle interventions have been consistent in different ethnic groups and settings[52,55,66,72-74] and for people with increased diabetes risk (eg, women with a history of gestational diabetes[75] and participants with high levels of insulin resistance[76]). In addition, an analysis of the DPP study population[52,55] showed that lifestyle interventions can overcome genetic susceptibility to T2DM, further supporting the importance of lifestyle change for diabetes prevention.[77] It is important to note, however, that each of the 4 randomized trials of lifestyle interventions for diabetes prevention was conducted in participants with impaired glucose tolerance. Although it is yet to be seen if these results extend to all people with prediabetes, lifestyle participants in the DPP had an increase in fasting glucose over time that was significantly lower than that found in the placebo group (although fasting glucose increased over time in all study groups),[52] indicating that lifestyle change might also be effective for individuals with IFG.

The estimated annual increase in expenditures attributed to diabetes for a person in the United States is $6649 per year.[78] Statistical analyses of the DPP, the DPS, and the Indian Diabetes Prevention Programme have projected the lifestyle intervention in each program to be cost-effective.[79-81] For example, in the DPP, the cost of the lifestyle intervention from a societal perspective was $24 400 per case of diabetes delayed or prevented, less than the cost per case of diabetes prevented or delayed for metformin ($34 500); from the perspective of the health system, compared with placebo, the cost was $15 655 per case of diabetes prevented for the lifestyle intervention and $31 338 per case of diabetes prevented for metformin.[81]

Based on the findings of these and other studies, expert organizations, including the European Society of Cardiology and European Association for the Study of Diabetes,[82] the Canadian Diabetes Association,[83] the American Diabetes Association,[84] and the International Diabetes Federation,[85] recommend lifestyle changes such as weight loss and increased physical activity for the prevention of T2DM among those with prediabetes.

Lifestyle Interventions and Management of T2DM

Lifestyle interventions have been similarly helpful in improving health in T2DM patients. T2DM patients receiving lifestyle interventions in community or clinical settings exhibit improvements in resting energy expenditure, low-density lipoprotein (LDL) cholesterol, insulin sensitivity, and weight loss as well as decreases in HbA1c, BMI, blood pressure, and fasting glucose.[86-92] In one trial, physicians were asked to counsel their T2DM patients about lifestyle changes at a baseline visit and over the phone in the following months. Patients who increased their levels of physical activity the most based on these interactions had improvements in health outcomes (significant reductions in weight, BMI, waist circumference, fasting plasma glucose, heart rate, and LDL; significant increases in high-density lipoprotein (HDL) cholesterol; and a 4% to 5% reduction in 10-year coronary heart disease risk) and significant reductions in medical and indirect social costs related to T2DM.[93]

The Look AHEAD (Action for Health in Diabetes) study randomly assigned overweight and obese subjects with T2DM to receive either usual care or an intensive lifestyle intervention that focused on weight loss and increased physical activity. The lifestyle intervention included group-based classes, individual monthly meetings with a lifestyle counselor, calorie reduction through diet change and a liquid meal replacement plan, and increased physical activity. In addition, the Look AHEAD lifestyle intervention program prescribed a weight-loss drug, orlistat, to select participants.[94] Lifestyle intervention participants lost significantly more weight than those in the control group (8.6% ± 6.9% weight loss vs 0.7% ± 4.8% weight loss). The odds of reaching the weight loss goal of 7% were highest for participants in the highest quartiles of physical activity, consumption of meal replacements, and attendance at study classes. High self-reported physical activity correlated the strongest with weight loss.[95]

Furthermore, the effects of these interventions are also beneficial for the families of T2DM patients. Spouses of participants in the Look AHEAD intensive lifestyle intervention lost more weight, had greater reductions in total energy and total energy from fat, and reported more low-fat and less high-fat foods in their homes than spouses of control participants.[96] Current trials of lifestyle interventions for people with T2DM are under way in the United States[97] and abroad[98] and will add to the literature on the long-term effects of these programs for improvements in diabetes care and on secondary prevention.

Why Are Lifestyle Interventions Beneficial?

Excess weight and obesity are strongly related to risk for T2DM,[99] and lifetime diabetes risk increases with increasing BMI.[100] Among all age groups, BMI above the normal-weight range is associated with an increased risk for development of T2DM,[101] and diabetes risk increases by 12% for each unit of BMI increase.[102] Conversely, a 10% weight loss reduces the risk of T2DM by 0.5% to 1.7% (depending on gender, BMI, and age).[103]

Weight loss, changes in body fat distribution and increases in physical activity (independent of weight loss) have been shown to be determinants of T2DM risk reduction in lifestyle intervention trials.[104-106] In the DPS, lifestyle intervention participants showed significant decreases in sedentary behavior and increases in moderate to vigorous physical activity, decreases in total and saturated fat, and increases in fiber compared with controls.[57] Increases in moderate to vigorous and strenuous physical activity were associated with a 63% to 65% reduction in diabetes risk.[104] In addition, a low-fat, high-fiber diet had a dose-dependent association with sustained weight loss and was also associated with reduced diabetes risk.[107] In the DPP lifestyle intervention

group, BMI, waist and hip circumference, weight, and waist-to-hip ratio predicted diabetes incidence in both sexes, and diabetes risk reduction in the lifestyle intervention arm was significantly predicted by weight, BMI, and waist reduction in women and by weight, BMI, waist-to-hip ratio, waist circumference, and subcutaneous and visceral fat reduction in men.[106] In obese patients with T2DM, decreasing intake of simple sugars alone (without weight loss) results in improvements in glycemic control.[108]

Incorporating Lifestyle Advice Into Clinical Care

The lifestyle interventions used in the randomized trials discussed above have the following common components:

- lessons or information on behavior change that use existing behavioral theories, for example, Prochaska's Stages of Change Model[109];
- physical activity education and a weekly physical activity prescription of at least 150 minutes per week;
- dietary education and advice to follow a well-balanced diet rich in whole grains, fruit, and vegetables with <30% total fat and no more than 10% saturated fat; and
- a weight loss of at least 5% to 7%.

Providing patients with ideas and tools to help them succeed in making these lifestyle changes will result in improvements in their long-term health. First, it is important to assess and address the patient's self-efficacy for the behavior changes. Self-efficacy, an individual's self-perception of his or her ability to change, is a mediator of behavior change.[110] In the DPP, exercise self-efficacy was significantly and positively correlated with mean leisure-time physical activity throughout the study.[111] Patients with low self-efficacy for changing diet or increasing physical activity should be encouraged and provided with information or resources to aid them in their attempts at change.

In addition, research has indicated that patients with higher BMI, anxiety, depression, or stress might require extra support and encouragement to make and sustain behavior changes.[111] Social support, such as that provided in group-based weight loss programs or walking groups, is an effective tool to help people succeed in making and sustaining behavior changes[112] and could be used to help patients at greatest risk of failing in their attempts at lifestyle change.

To change behavior, individuals must have the ability to problem solve and the tools to overcome barriers to behavior change. For patients to be able to use the lifestyle advice given to them, health care providers should help patients to identify barriers and brainstorm ways to deal with these barriers.[113] For example, if a patient reports that he or she eats out frequently, the health care provider could help them identify healthy foods on the menu and empower him or her to talk to the server about making substitutions.

Lifestyle messages should be culturally appropriate to improve acceptability and adherence. When people are approached in a culturally sensitive way, they are more receptive to health messages.[114,115] In addition, culturally appropriate advice can be easier to use immediately, as participants do not have to modify the advice on their own to account for common food and activity choices in their community. Culturally appropriate online resources from expert groups such as the American Diabetes Association and others can be used for different patient populations.

Many patients might be overwhelmed by attempts to modify both diet and physical activity simultaneously. Because physical activity has been shown to improve adherence to diet change, teaching physical activity first in these cases is advisable. In the Early ACTivity in Diabetes study, patients with T2DM taught simultaneously about physical activity and diet reported that they used physical activity to support diet change. These participants reported that physical activity allowed them to offset "cheats and treats" in their diet by including extra activity sessions or time; improved mental and physical health, thereby making it easier to implement dietary changes; and helped them to control their blood glucose level.[116] In addition, exercise alone seems to be an important component of diabetes prevention. As mentioned above, exercise is an independent predictor of diabetes risk reduction in lifestyle intervention programs, and in the Da Qing Diabetes Prevention Study, intervention groups with exercise education alone or diet + exercise education had a slightly greater reduction in diabetes risk compared with controls than the group with diet education alone, although these differences were nonsignificant.[56]

Regular physical activity is low in T2DM populations.[117] For patients who are reluctant to participate in an exercise program or for whom exercise is new, gradually increasing their exercise prescription until they are participating in the recommended amount of physical activity will likely increase adherence and acceptibility.[118] Both home-based and gym-based training programs have been shown to be effective in improving health outcomes.[72] In addition, programs including both endurance and resistance exercises increase compliance by allowing participants to do a variety of exercises[119]; in T2DM patients and patients with IGT, doing both types of exercise enhances insulin sensitivity compared with aerobic exercise alone.[88]

Short-term interventions of increased, moderate-intensity exercise have been demonstrated to increase fitness level[120,121] and reduce cardiovascular[122-125] and diabetes[126,127] risk factors. Pedometers are inexpensive, easy to use, encourage monitoring and improvement in daily physical activity levels, and allow for an immediate, ongoing assessment of daily physical activity goals. They require minimal effort and are compatible with most activities of daily life.[128] Pedometers have been shown to increase physical activity levels in T2DM patients.[86] In the PREPARE (Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement) Programme, overweight or obese individuals with IGT were randomized to receive a control intervention or a single, group-based education program with or without pedometers.

Two-hour glucose decreased significantly at 3 and 12 months and fasting glucose decreased significantly at 3, 6, and 12 months in the pedometer group compared with the control group at 3 and 12 months. In the intervention group without pedometers, there was no significant difference in fasting or 2-hour glucose at any time point. Furthermore, self-reported overall moderate-to-vigorous activity and walking was significantly greater for the pedometer group compared with the control group at all time points.[129]

Resistance training (RT), which has long been touted for its strength-enhancing effects, has recently been recognized for its relationship to health and disease risk. Moderate- to high-intensity RT performed 2 to 3 days per week is associated with improvements in cardiovascular disease risk factors in the absence of significant weight loss. The addition of muscle-strengthening exercises to a weight loss program may help conserve free fat mass and basal energy while facilitating weight loss management. When paired with regular aerobic physical activity, RT may represent a feasible exercise intervention to promote healthy body composition and prevent excess adiposity.[130]

Similar to increasing physical activity, dietary changes can be made gradually over time, starting with small behavior changes (eg, eating fried foods only on occasion or switching from white to whole-grain breads). A prospective analysis of the Whitehall II cohort compared an unhealthy diet pattern (full-fat dairy products, refined grains, processed meat, and fried foods) with a sweet dietary pattern (high-fat dairy, dessert items, processed meats, and refined grains), a Mediterranean-like diet (fruits and vegetables, rice, pasta, and wine), and a healthy diet (low-fat dairy, whole grains, fruits and vegetables, and moderate alcohol). The authors found that compared with the unhealthy diet, the healthy diet, a low-fat diet rich in fiber, reduced the 15-year risk of diabetes, death from a coronary event, or nonfatal myocardial infarction. Only the healthy diet significantly reduced diabetes risk; the hazards ratio for diabetes risk reduction comparing the healthy diet to the unhealthy diet was 0.71 (95% confidence interval, 0.51-0.98).[131] Diets reduced in glycemic index and glycemic load may also be useful in helping prevent the development of T2DM.[132] For patients with T2DM, diets low in saturated fat and high in unsaturated fat and high in fruit, vegetable, and fiber intake (eg, the Mediterranean diet) have also been shown to be beneficial for glucose control compared with diets with higher contents of simple sugars and carbohydrates.[133]

Many resources are available for patients from organizations such as the American Heart Association, providing diet advice, meal plans, recipes, and tips consistent with a low-fat, high-fiber diet. A recent study by Liese and colleagues[134] showed that following the DASH (Dietary Approaches to Stop Hypertension) dietary pattern (a low-fat, high-fiber diet rich in vegetables, fruit, and low-fat dairy products) was inversely associated with diabetes risk. For patients requiring more guidance on diet change, a registered dietician can provide individualized advice.

Patients at Particular Risk

Because lifestyle interventions may not prevent the development of diabetes in individuals whose prediabetes involves a more severe β-cell defect, it is vital that physicians continue to monitor their patients. For some patients who enact lifestyle change later in their natural history of glucose intolerance, glucose-lowering drugs might be needed earlier to complement the effect of lifestyle interventions to reduce insulin resistance. An American Diabetes Association consensus statement recommends that individuals with both IFG and IGT and 1 additional risk factor for progression to diabetes (age <60 years, BMI ≥35 kg/m^2, family history of diabetes in a first-degree relative, elevated triglycerides, reduced HDL cholesterol, or HbA1c >6.0%) should be considered for treatment with metformin, in addition to lifestyle modification.[135]

Our studies indicate that up to 24 million Americans may be at high risk of developing diabetes by this definition,[136] so this is not a rare problem. Moreover, the prevalence of high risk is 25% in patients with IFG and FPG 100 to 109 mg/dL and 50% in patients with IFG and FPG 110 to 125 mg/dL; thus, patients with IFG should have an OGTT to see if they are at particular risk.

Conclusion

In conclusion, T2DM is a major public health problem in the United States and worldwide. The rising prevalence of diabetes is due primarily to secular trends in lifestyle choices (decreasing physical activity and increasing body weight), which increase insulin resistance. Fortunately, insulin resistance can be decreased by lifestyle intervention programs. Lifestyle interventions, programs promoting behavior changes for weight loss, improvement in diet quality, and increased physical activity, have been shown to reduce diabetes incidence in high-risk populations and are effective tools for improving the health of people with T2DM. Clinicians should advise patients at risk of developing T2DM and patients already diagnosed with T2DM to modify their lifestyle by providing them with culturally appropriate tools and social support while continuing to monitor glucose levels to chart patients' progress and identify deteriorations in glucose tolerance that might signal a need for pharmacologic therapy.[26]

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