Prevention of Type 2 Diabetes: Evidence and Strategies
Jocelyne G. Karam, MD, and Sany I. McFarlane, MD, MPH, MBA

ABSTRACT

• **Objective.** To discuss the epidemic of diabetes highlighting the natural history of the disease and the major clinical trials aimed at diabetes prevention in different prediabetic populations around the world.

• **Results.** Diabetes prevention studies have evaluated various interventions including lifestyle modifications, metformin, alpha-glucosidase inhibitors, thiazolidinediones, nateglinide, and xenical as well as the renin-angiotensin aldosterone system (RAS) inhibitors. Lifestyle modifications seem to be the safest, most effective, and most sustainable intervention to prevent diabetes. Except for metformin, the potential diabetes prevention benefits of the studied pharmacologic agents are limited by safety concerns or lack of durable efficacy or tolerability. RAS blockade and fibrates have a favorable glycemic effect, and, when indicated, are reasonable treatment options for hypertension and hyperlipidemia in prediabetic patients.

• **Conclusion.** As recommended by American Diabetes Association guidelines, patients with prediabetes should be referred to an intensive diet and physical activity behavioral counseling program; diet and activity goals include a loss of 7% of body weight and at least 150 minutes of moderate physical activity per week. Metformin therapy for diabetes prevention should be considered as well.

**Key words:** prediabetes; type 2 diabetes mellitus, diabetes prevention, lifestyle modifications.

**Diabetes mellitus** has reached pandemic proportions across the globe. The International Diabetes Federation (IDF) estimates that in 2015 around 415 million people, or 1 in 11 adults, had diabetes, compared to 285 million in 2010, with 5 million deaths, or 1 death every 6 seconds, occurring because of diabetes or diabetes complications [1]. In the United States, an estimated 29.1 million Americans, or 9.3% of the population, have diabetes, 27.8% of them undiagnosed [2]. The prevalence of diabetes increases significantly with age, affecting around 16.2% of American adults aged 45 to 64 years and 25.9% of adults aged 65 years or older [2]. The Centers for Disease Control and Prevention (CDC) estimates that, with current trends, as many as 1 in 3 American adults could have diabetes by 2050 [3].

Type 2 diabetes mellitus (T2DM) accounts for the majority of prevalent and newly diagnosed diabetes in the world, and is strongly linked to overweight and inactivity in adults [4]. T2DM is increasingly being diagnosed in pediatric patients, in whom type 1 diabetes has historically been predominant; it now accounts for approximately 30% of newly diagnosed diabetes in children aged 10 to 19 years, exceeding 50% in certain ethnicities such as non-Hispanic black and American Indian/Alaska Native children [2].

These alarming trends have spurred significant research and public efforts aimed at reducing the prevalence of diabetes by preventing T2DM. Indeed, insulin resistance and abnormal carbohydrate metabolism progress over many years prior to the diagnosis of diabetes and manifest with different clinical and biochemical features. Both the pathophysiology and the natural history of T2DM offer clinicians an opportunity to identify patients at risk for developing the disease and to implement prevention strategies. This article outlines the risk factors and diagnostic criteria for prediabetes, describes the studies that have explored diabetes prevention through lifestyle changes, pharmacotherapy, or surgery, and reviews recommendations for managing patients at risk.

**Risk Factors and Screening for T2DM**
Identifying risk factors for diabetes is a necessary step in screening individuals and taking measures to prevent...
diabetes (Table 1). Nonmodifiable risk factors include age (≥ 45 years), family history of diabetes in a parent or a sibling, personal history of gestational diabetes, history of polycystic ovary syndrome, and ethnicity (ie, Native American, African American, Hispanic American, or Pacific Islanders). Obesity, physical inactivity, dyslipidemia, hypertension, smoking, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) constitute modifiable risk factors for T2DM [5]. Excessive weight, specifically abdominal obesity, is thought to be a major contributor to the rising prevalence of T2DM across different ethnic and age groups [6]. Indeed, obesity is at the core of the metabolic syndrome, which manifests with increased waist circumference, high blood pressure, high triglycerides, low high-density lipoprotein (HDL) cholesterol, and/or abnormal glucose metabolism. The association between metabolic syndrome and an increased risk for diabetes is very well established [7].

The American Diabetes Association (ADA) recommends screening all adults for prediabetes by assessing for diabetes risk factors [8]. Glucose testing is recommended in individuals aged 45 years or older, and should be considered in adults of any age who are overweight or obese (body mass index [BMI] ≥ 25 kg/m² or ≥ 23 kg/m² in Asian Americans) and have 1 or more additional risk factors for diabetes. Testing also should be considered in children and adolescents who are overweight or obese and who have 2 or more additional risk factors. If tests are normal, repeat testing carried out at a minimum of 3-year intervals is suggested [8].

Prediabetes
Abnormalities in glucose metabolism progress along a continuum through various stages before T2DM develops. Years before the development of overt diabetes, and especially in the presence of excessive visceral fat, cellular sensitivity to insulin gradually decreases, leading to a compensatory increased insulin secretion [9]. With time, and under continuous increased demand, pancreatic beta cell function declines and ultimately fails to overcome insulin resistance and maintain a normal glucose metabolism, resulting in prediabetes followed by the development of diabetes. This early beta cell dysfunction was illustrated by the decreased beta cell volume observed on autopsy of obese patients with IFG or T2DM, when compared to obese individuals with normal glucose tolerance [10]. It is estimated that around 40% to 70% of beta cell function is already lost by the time diabetes is clinically diagnosed. This relatively slow pathophysiologic process allows the identification of at-risk patients well before their blood glucose levels reach the diabetic diagnostic thresholds, and therefore presents an opportunity for prevention.

**Diagnostic Criteria**
The ADA guidelines released in 2003 define prediabetes as IFG (fasting blood glucose [FBG] levels of 100–125 mg/dL), IGT (glucose levels of 140–199 mg/dL at 2 hours during an oral glucose tolerance test [OGTT] following an oral load of 75 g of dextrose), or both. Additionally, hemoglobin A1C (A1C) was introduced as a diagnostic tool for prediabetes in 2010, with values between 5.7% and 6.4% indicating prediabetes [8]. Most of these thresholds were chosen due to their association with increased rates of complications, notably retinopathy and cardiovascular disease.

A combined report from the World Health Organization (WHO) and the IDF published in 2006 defined intermediate hyperglycemia as IFG, but with a higher cutoff for FBG (110–125 mg/dL) than the ADA's definition, and/or IGT (2-hour OGTT glucose level of 140–199 mg/dL) [11]. The rationale for a higher cut-point for IFG is the concern about the increased prevalence of IFG and its impact on individuals and health systems and the more favorable cardiovascular risk profile and decreased risk of progression to diabetes in the group of patients with FBG of 100 to 110 mg/dL when compared to the group with FBG of 110 to 125 mg/dL. The report does not recommend the use of

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**Table 1. Risk Factors for Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Nonmodifiable risk factors</th>
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<tbody>
<tr>
<td>Age &gt; 45 yr</td>
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<tr>
<td>First-degree family history of type 2 diabetes</td>
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<tr>
<td>High-risk ethnicity (eg, Native American, African American, Hispanic American, Pacific Islander)</td>
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<tr>
<td>History of gestational diabetes</td>
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<tr>
<td>History of polycystic ovary syndrome</td>
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</tbody>
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<table>
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<tr>
<th>Modifiable risk factors</th>
</tr>
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<tbody>
<tr>
<td>Overweight/obesity</td>
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<tr>
<td>Sedentary lifestyle</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Smoking</td>
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</table>
A1C in the diagnosis of diabetes or intermediate hyperglycemia because of a lack of global consistency and the potential for other factors that can be prevalent in some developing countries, such as hemoglobinopathies and anemia, to interfere with the assay.

Prevalence and Progression to Diabetes

According to CDC data from 2014, up to 86 million American adults, more than 1 in 3, have prediabetes, and 9 out of 10 of these individuals are undiagnosed [2]. It is estimated that approximately 25% of people diagnosed with either IFG or IGT progress to diabetes mellitus over a 3- to 5-year period [12]. If observed for longer periods, most prediabetic persons will probably develop diabetes. The highest rate of progression to diabetes is observed in patients with both IFG and IGT, older age, overweight, or other diabetic risk factors.

Complications

In addition to increasing the risk for progression to diabetes, prediabetes is independently associated with microvascular and macrovascular complications and increased risk of death, prior to the actual onset of diabetes. The DECODE study demonstrated significantly increased mortality in 2766 individuals with IGT after 7 years of follow-up, when compared to normoglycemic patients; this effect was more prominent in participants with IGT than in participants with IFG [13]. In the Australian Diabetes, Obesity and Lifestyle Study, IFG was found to be an independent predictor for cardiovascular mortality after adjustment for age, sex, and other traditional cardiovascular risk factors [14].

Similarly, a recent meta-analysis demonstrated that the presence of IFG was significantly associated with future risk for coronary heart disease (CHD), with the risk increase starting when fasting plasma glucose was as low as 100 mg/dL; however, this finding may have been confounded by the presence of undetected IGT or other cardiovascular risk factors [15]. Another recent systematic review of 53 prospective cohort studies with 1,611,339 participants showed that prediabetes (IFG or IGT) was associated with an increased risk of composite cardiovascular disease, CHD, stroke, and all-cause mortality [16].

The association between retinopathy and prediabetes has been described in multiple reports and this association has helped guide authors on selected thresholds for diagnosis of prediabetes. For example, in 1 study, the incidence of retinopathy in individuals with IGT was 12% among Pima Indians [17]. Similarly, in a follow-up study of the Diabetes Prevention Program, 8% of prediabetic participants who remained nondiabetic had evidence of retinopathy [18].

Neuropathy also has been observed in prediabetes. A noninvasive neurologic evaluation of individuals with IGT revealed subclinical neural dysfunction suggestive of cardiovascular autonomic neuropathy [19]. At the clinical level, a study that evaluated 100 patients with chronic idiopathic axonal neuropathy of unknown etiology found IFG in 36 and IGT in 38 patients, underscoring the role of abnormal glucose metabolism in these patients [20].

Nephropathy may also be more prevalent in those with prediabetes. In a 1999–2006 National Health and Nutrition Examination Survey analysis, the adjusted prevalence of chronic kidney disease, defined by estimated glomerular filtration rate (eGFR) of 15 to 59 mL/min per 1.73 m² or albumin-creatinine ratio ≥ 30 mg/g, was 17.1% in individuals with IFG, compared to 11.8% in individuals with normal fasting glucose [21].

Due to the increased risk for progression to diabetes posed by prediabetes and the evidence of associated microvascular and macrovascular complications, along with the enormous public health scale, researchers have investigated many diabetes prevention strategies in persons at risk, including lifestyle modifications, pharmacotherapy, and surgery (Table 2 and Table 3).

Lifestyle Modifications

The alarming rapid increase in the prevalence of T2DM has been linked to a parallel rising epidemic of overweight, obesity, and lack of physical activity. Therefore, lifestyle changes aiming at weight reduction seemed to be a natural individual and public health strategy to prevent diabetes, and such strategies have been the focus of many randomized controlled trials around the world. As anticipated, weight loss, exercise, and diet have all been shown, separately or in combination, to be effective in decreasing the incidence of T2DM in high-risk patients [22–27]. Furthermore, and well beyond the benefit observed during the trials, follow-up studies revealed a sustained reduction of diabetes incidence in intervention groups several years after cessation of the intervention [28–32] (Table 2).

The Da Quing Diabetes Prevention Study (DQDPS), published in 1997, is one of the earliest prospective diabetes prevention trials [22]. This 6-year study conducted in 33 clinics in China from 1986 through 1992 included 577 participants with IGT who were randomly assigned
to 1 of 4 groups: (1) diet (high vegetables, low sugar/alcohol) only, (2) exercise, (3) diet plus exercise, and (4) standard of care. At 6 years, diabetes incidence was significantly reduced by 46% in the exercise group, 31% in the diet group, and 42% in the diet plus exercise group compared to standard care. In 2006, 14 years after the end of the trial and 20 years after the initial enrollment, the cumulative incidence of diabetes was significantly lower in the intervention group at 80%, compared to 93% in the control group, and the annual incidence of diabetes was 7% and 11%, respectively, with a 43% lower incidence of diabetes over the 20-year period in the combination lifestyle changes group [28].

The preventive benefit of lifestyle changes persisted 2 decades after the initial randomization despite the standardization of treatment for all groups over the 14 years following the study, suggesting a strong and longitudinal preventive effect of the initial lifestyle modifications. In a follow-up study of the DQDPS conducted in 2009, at 23 years of follow-up, the cumulative incidences of cardiovascular mortality and all-cause mortality were significantly lower in the intervention group (11.9% versus 19.6%, and 28.1% versus 38.4%, respectively), highlighting the long-term clinical benefits of lifestyle intervention in patients with IGT [29].

Similarly, the Finnish Diabetes Prevention Study (FDPS), published in 2001, enrolled 522 middle-aged overweight participants with IGT [23]. The participants randomly assigned to the intervention group received individualized counseling designed to reduce weight, decrease total intake of fat and saturated fat, increase intake of fiber, and increase physical activity. The control group received standard therapy. At 4 years of follow-up, the cumulative incidence of diabetes was 11% in the intervention group and 23% in the control group, with a statistically significant 58% reduction in risk for progression to diabetes. A follow-up of the FDPS was published in 2006 [31]. Participants who did not progress to diabetes in the initial 4-year study were further followed for a median of 3 years. Interestingly, lifestyle changes were maintained by the intervention group participants despite the cessation of the individual counseling, leading to a 36% relative reduction in diabetes incidence during the post-intervention follow-up period alone.

### Table 2. Major Lifestyle and Metformin Diabetes Prevention Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country</th>
<th>Year</th>
<th>Population</th>
<th>No.</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>RRR (vs Control), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DQDPS [22]</td>
<td>China</td>
<td>1997</td>
<td>IGT</td>
<td>577</td>
<td>6 yr</td>
<td>Diet</td>
<td>31</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Exercise</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diet + exercise</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>F/U DQDPS [28]</td>
<td>China</td>
<td>2014</td>
<td>IGT</td>
<td>577</td>
<td>20 yr</td>
<td>Combined lifestyle</td>
<td>46</td>
</tr>
<tr>
<td>FDPS [23]</td>
<td>Finland</td>
<td>2001</td>
<td>IGT</td>
<td>522</td>
<td>4 yr</td>
<td>Lifestyle modifications</td>
<td>58</td>
</tr>
<tr>
<td>F/U FDPS [31]</td>
<td>Finland</td>
<td>2006</td>
<td>IGT</td>
<td>522</td>
<td>7 yr</td>
<td>Lifestyle modifications</td>
<td>43</td>
</tr>
<tr>
<td>DPP [24]</td>
<td>US</td>
<td>2002</td>
<td>IFT or IGT</td>
<td>3234</td>
<td>3 yr</td>
<td>Lifestyle modifications</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metformin</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>DPPOS [32]</td>
<td>US</td>
<td>2009</td>
<td>IFT or IGT</td>
<td>3234</td>
<td>10 yr</td>
<td>Lifestyle modifications</td>
<td>34</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Metformin</td>
<td></td>
<td>18</td>
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<tr>
<td>IDPP-1 [26]</td>
<td>India</td>
<td>2006</td>
<td>IGT</td>
<td>531</td>
<td>3 yr</td>
<td>Lifestyle modification</td>
<td>28</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Metformin</td>
<td></td>
<td>26</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lifestyle + metformin</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Zensharen [27]</td>
<td>Japan</td>
<td>2011</td>
<td>IFT</td>
<td>641</td>
<td>3 yr</td>
<td>Lifestyle modification</td>
<td>26 (in IFT + IGT + ↑ A1C)</td>
</tr>
</tbody>
</table>

DPP = Diabetes Prevention Program; DPPOS = DPP Outcome Study; DQDPS = Da Quing Diabetes Prevention Study; FDPS = Finnish Diabetes Prevention Study; IDPP = Indian Diabetes Prevention Program; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; RRR = relative risk reduction.
Prevention of Type 2 Diabetes

(4.6 vs 7.2 per 100 person-years, $P = 0.041$) and a 43% cumulative diabetes incidence reduction over the 7-year follow-up, demonstrating, one more time, the sustained efficacy of lifestyle changes.

In the United States, the Diabetes Prevention Program (DPP) trial is a landmark NIH-sponsored multicenter randomized controlled trial published in 2002, and one of the largest diabetes prevention studies with lifestyle changes to date [24]. A total of 3234 participants with prediabetes, defined as an IFG or IGT, were randomly assigned to an intensive lifestyle modification program, metformin 850 mg twice daily, or matching placebo. Lifestyle changes included a low-fat (< 25% of caloric intake), 1200- to 1800-calorie diet and exercise for 150 minutes a week, with a 7% body weight reduction goal and a very well structured curriculum and professional support group. The study was discontinued early (at 3 years) as the data demonstrated the superiority of lifestyle changes, with a 58% reduction in diabetes incidence in the lifestyle intervention group and a 31% reduction in the metformin group when compared to placebo (cumulative incidence of diabetes at 3 years of 28.9%, 21.7 %, and 14.4% in the placebo, metformin, and lifestyle intervention groups, respectively). Lifestyle changes were significantly more effective than metformin and were consistently effective in men and women across age, BMI, and ethnic groups.

The DPPOS (DPP Outcome Study) was a 10-year follow-up of the DPP study published in 2009 where all participants were offered group-implemented lifestyle changes and were followed for an additional 5.7 years [32]. Unlike the Finnish follow-up study, diabetes incidence was similar in the 3 treatment groups in the follow-up period. However, the cumulative incidence of diabetes remained significantly the lowest in the original lifestyle group, with a 34% cumulative risk reduction in the lifestyle group and an 18% reduction in the metformin group at 10 years when compared to placebo. Interestingly, unlike
most other studies of weight-reducing interventions, in the DPPOS, patients in the lifestyle changes and metformin groups maintained weight loss at 10 years' follow-up.

In Japan, a diabetes prevention study assigned 458 male participants with IGT to a standard intervention group or an intensive intervention group receiving detailed lifestyle modification counseling every 3 to 4 months during hospital visits [25]. The cumulative 4-year incidence of diabetes was 9.3% in the control group versus 3.0% in the intervention group, and the reduction in diabetes risk was 67.4% \((P < 0.001)\), with body weight reductions of 0.39 kg and 2.18 kg, respectively \((P < 0.001)\). Of note, participants with higher FBG at baseline developed diabetes at a higher rate than those with lower values. This study suggested that lifestyle change counseling conducted in an outpatient clinic setting can be very effective in preventing diabetes.

Indian adults are thought to be more insulin resistant at a younger age and at a lower BMI than Caucasians. To assess whether the DPP findings can be replicated in an Indian population, the Indian Diabetes Prevention Program (IDPP) trial randomized a total of 531 participants with IGT to 4 groups: control, lifestyle modification, metformin, and lifestyle modifications with metformin [26]. The 3-year cumulative incidences of diabetes were 55.0%, 39.3%, 40.5%, and 39.5%, respectively, showing again a significant relative reduction in progression to diabetes of 28.5% with lifestyle changes, 26.4% with metformin, and 28.2% with both lifestyle changes and metformin, as compared with the control group.

In a Japanese unmasked, multicenter, randomized controlled trial published in 2011, 641 overweight adults with IFG were randomized to a frequent intervention group, receiving individual counseling and support for lifestyle modifications 9 times over 36 months, or a control group, receiving counseling 4 times over the same period. The 3-year cumulative incidence of T2DM was significantly lower in the frequent intervention group than in the control group (12.2% vs 16.6%) [27]. Interestingly, in a posthoc subgroup analysis, the protective effect was more prominent in patients with underlying associated IGT or elevated A1C, but was not observed in patients with isolated IFG, suggesting a possible prognostic value of an additional A1C or oral glucose tolerance test in individuals with IFG.

**Diet**

The diet followed in the major diabetes prevention trials discussed above has typically been a weight-reducing diet with decreased fat intake (eg, DPP, Da Quing, DPP, Finnish trials) and increased fiber intake (eg, Da Quing, DPP, Finnish trials). However, there has been more emphasis recently on the importance of the quality rather than the quantity of fats in preventing diabetes. For example, in a Spanish study, a non–calorie-restricted traditional Mediterranean diet, enriched with high-fat foods of vegetable origin (olive oil, nuts) decreased the incidence of diabetes by 52% in individuals at high cardiovascular risk after a median follow-up of 4.0 years, and in the absence of significant changes in body weight or physical activity among the groups [33]. These findings were reproduced by other studies. A recent meta-analysis examining the relation between intake of fruits and vegetables and the incidence of diabetes revealed that higher intake of fruit, especially berries, and green, leafy vegetables, yellow vegetables, cruciferous vegetables, or their fiber is associated with a lower risk of T2DM [34].

**Exercise**

Exercise is thought to improve insulin sensitivity and promote peripheral glucose uptake in normal individuals. Long-term moderate exercise, similar to the exercise recommended in DPP and FDPS, results in increased translocation of insulin-responsive glucose transporter (GLUT-4) from intracellular stores to the cell surface, facilitating glucose uptake [35]. A systematic review of 10 prospective cohort studies published in 2007 showed that, after adjustment for BMI, moderate-intensity physical activity was significantly associated with reduced diabetes incidence [36]. In the FDPS, participants who achieved at least 4 hours of exercise per week had a significant 80% decrease in incidence of diabetes, and this effect was observed even in the group that did not lose weight [23]. In the DQDPS, the greatest reduction in diabetes incidence was observed in the exercise group [22].

In a recent NIH-funded trial designed to examine the relative contribution of exercise alone to the overall beneficial effect of lifestyle changes in the DPP study, a total of 237 adults with IFG were randomly assigned to 4 different groups: low-amount moderate intensity exercise (similar to exercise followed in DPP), high-amount moderate intensity exercise, high-amount vigorous intensity exercise, and a combination of diet, weight loss, and low-amount moderate exercise. Only the diet and exercise group experienced a decrease in fasting glucose, whereas similar improvements in glucose tolerance were observed in both the diet and exercise group and the high-amount...
moderate-intensity exercise group, suggesting that such an exercise regimen may be as effective as a more intensive multicomponent approach involving diet, exercise, and weight loss for preventing diabetes [37].

**Weight Loss**

Weight reduction in prediabetic individuals has been consistently associated with reduced incidence of diabetes. Furthermore, the amount of weight loss needed to achieve this benefit seems to be relatively modest and a realistic goal to set for patients. Indeed, in the DPP trial, an average weight loss of only 5.6 kg was associated with a 58% lower incidence of diabetes [24]. Moreover, on further analysis of the DPP trial, and among weight, diet, and exercise, diabetes prevention correlated most strongly with weight loss, with an estimated 16% diabetes risk reduction for every single kilogram of weight reduction [38]. Similarly, within the same lifestyle intervention group in the FDPS, the participants who were able to achieve an initial body weight loss greater than 5% at 1 year had a nearly 70% relative risk reduction in progression to diabetes, when compared to their peers in the intervention group who had less or no weight loss [23].

In summary, numerous randomized controlled studies from various populations have proved that lifestyle modifications, including healthy diet, moderate weight loss, and moderate-intensity exercise, represent a very effective strategy to prevent diabetes in patients at risk, mostly patients with IGT, and this protective effect seems to be sustained over time.

**Pharmacologic Interventions**

**Metformin**

Metformin is an antidiabetic agent that works mostly at the liver site by suppressing hepatic glucose production and inhibiting production and oxidation of free fatty acids (FFA), thereby reducing FFA-induced insulin resistance and promoting peripheral glucose uptake [39]. This effect has the potential of preserving beta cell function by reducing the demand for insulin secretion.

In the DPP trial, metformin, although generally less effective than lifestyle changes, was associated with a significant 31% reduction in diabetes incidence (cumulative incidence of 22% in metformin group vs 29% in placebo group) and significant weight reduction (average of 2 kg) [24]. Further analysis of the DPP results showed that metformin efficacy, compared to placebo, was greater in patients who were younger, had higher BMI, and had higher FBG levels. In addition, a DPP substudy of 350 women with history of gestational diabetes and IGT revealed that this group of women, who had a higher risk of progression to diabetes (71% at 3 years) when compared to women with no history of gestational diabetes, despite similar baseline glucose levels, had similar diabetes risk reduction of 50% with both metformin and lifestyle changes [40].

In the IDPP study, both lifestyle changes and metformin reduced significantly and similarly the incidence of diabetes in adults with IGT, with no observed added benefit from combining both interventions [26]. It has not been clear, however, how much of this effect of metformin is a result of pharmacologic properties masking hyperglycemia or a true protective and preventive effect. In a washout study in which 1274 DPP participants who did not progress to diabetes underwent an OGTT after 1 to 2 weeks of discontinuing metformin or placebo, the incidence of diabetes was still reduced by 25% in the metformin group, after the washout period, compared to a 31% risk reduction in the primary DPP analysis, suggesting a partially sustained rather than temporary effect of metformin [41]. In the DPPOS long-term follow-up study, metformin (850 mg twice daily as tolerated) was continued in the group initially assigned to metformin in addition to lifestyle counseling [32]. Although the progression to diabetes was similar in all groups during the 5.7-year follow-up period, the cumulative incidence of diabetes at 10 years was still reduced in the metformin group by 18% when compared to control group. Furthermore, the weight loss associated with metformin was also interestingly sustained at 10 years. A meta-analysis echoed this beneficial effect of metformin observed in the DPP trial, reporting a relative risk reduction of new-onset diabetes of 40% with the use of metformin [42].

In summary, metformin has been shown to be effective in preventing diabetes in patients at risk, especially persons with younger age, higher BMI, and history of gestational diabetes and in native Asian Indians. The protective effect of metformin seems to be sustained over the long term in follow-up studies.

**Thiazolidinediones**

Thiazolidinediones (TZDs) are antidiabetic agents that have been evaluated in diabetes prevention trials. TZDs are peroxisome proliferator-activated gamma receptor (PPAR-γ) agonists that work by augmenting conversion of preadipocytes to adipocytes, which in turn increase
adiponectin levels, promoting insulin sensitivity [43]. In addition to their antihyperglycemic properties, TZDs are thought to have a direct protective effect on beta cells, potentially translating into prevention and delay of diabetes [44].

The first study to demonstrate diabetes prevention with a TZD was the TRIPOD study (Troglitazone in Prevention of Diabetes), in which 266 Hispanic women with a history of gestational diabetes were randomly assigned to troglitazone or placebo [45]. Troglitazone use was significantly associated with reduction of progression to diabetes at 1.5-year follow-up when compared to placebo (relative risk reduction of 55%), with a decrease of endogenous insulin requirement at 3 months of therapy and sustained benefit after discontinuation of the TZD, suggesting an effect on beta cell preservation.

Moreover, troglitazone was an investigational drug in the DPP trial from 1996 to 1998, at which time it was discontinued because of associated fatal liver failure in a DPP participant. In the DPP trial, troglitazone was associated with a remarkable 75% decrease in progression to diabetes at 1 year. Troglitazone was withdrawn from the US market in 2000 because of its association with severe hepatotoxicity.

The international DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medications) trial randomly assigned more than 5000 participants with IFG and/or IGT to rosiglitazone, ramipril, or placebo in a 2 × 2 factorial design [46]. In participants receiving rosiglitazone, the risk for progression to diabetes was reduced by 60% and the likelihood of regression to normoglycemia was increased by 71% when compared to placebo. However, the use of rosiglitazone was associated with an increased risk of new-onset congestive heart failure and a mean weight gain of 2.2 kg, thought to reflect increased subcutaneous gluteal fat deposition, with an observed decreased waist-to-hip ratio.

Interestingly, in a passive follow-up of the DREAM study conducted a median 1.6 years after the end of the trial and 4.3 years after randomization, participants treated with rosiglitazone had a 39% lower incidence of diabetes compared to placebo participants, and 17% more of them regressed from prediabetes to normoglycemia [47]. Nonetheless, there was no difference between the 2 groups when the analysis was restricted to the passive follow-up period, suggesting a time-limited exposure to rosiglitazone reduces the longer-term incidence of diabetes by likely delaying but not reversing the underlying disease process.

The third large trial assessing the efficacy of a TZD in preventing diabetes was the Actos Now for the prevention of diabetes (ACT NOW) trial, which was a randomized, double-blinded study that assigned 602 patients with IGT to pioglitazone 45 mg daily or placebo [48]. Over a median follow-up of 2.6 years, pioglitazone was associated with a 72% lower annual rate of progression to diabetes (2.1% compared to 7.6% in placebo group), and a higher rate of conversion to normal glucose tolerance (48%). In addition, pioglitazone had favorable effects on fasting and 2-hour blood glucose, A1C level, diastolic blood pressure, carotid intima thickness, and HDL cholesterol. As in the DREAM trial, an increased incidence of edema and weight gain was observed with pioglitazone.

Unlike the strong evidence supporting TZDs as an approach to diabetes prevention in the US trials, the Indian Diabetes Prevention Program-2 (IDPP-2) trial, which randomized 497 participants with IGT to lifestyle modifications with pioglitazone versus lifestyle modifications with placebo, did not demonstrate a significant reduction in diabetes at 3 years’ follow-up, suggesting a possible ethnicity-related variation in the effect of the medication [49]. In 2011, the French and German medications regulatory agency withdrew pioglitazone from the market because of a potential increase in incidence of bladder cancer with the cumulative use of more than 28 g of pioglitazone. In the United States, the Food and Drug Administration is performing an extensive review of data and advises against the use of pioglitazone in patients with a history of bladder cancer.

In summary, TZDs demonstrated significant efficacy in preventing diabetes in many patients at risk, but their safety concerns, particularly the associated new onset of congestive heart failure and potential increased risk of bladder cancer, might outweigh this benefit.

Combination Metformin and Thiazolidinediones

As metformin and rosiglitazone both have preventive benefits in diabetes, and rosiglitazone is associated with numerous side effects at a higher dose, a combination of metformin and low-dose rosiglitazone was evaluated in the CAnadian Normoglycemia Outcomes Evaluation (CANOE) trial [50]. A total of 207 patients with IGT were randomly assigned to receive combination metformin (500 mg twice daily) and rosiglitazone (2 mg daily).
Prevention of Type 2 Diabetes versus placebo for a median of 3.9 years. The combination therapy was associated with a 66% relative risk reduction of progression to diabetes.

**Alpha-glucosidase Inhibitors**

Alpha-glucosidase inhibitors are antidiabetic agents that slow oral carbohydrate intestinal absorption, subsequently improving postprandial hyperglycemia, which can eventually reduce glucose toxicity of pancreatic beta cells. In addition, they have been shown to improve insulin sensitivity in individuals with IGT [51] and have been found to exert a favorable protective effect in a prediabetic population [52]. In a multicenter placebo-controlled randomized trial, the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM), 1429 participants with IGT were randomly assigned to receive acarbose 100 mg 3 times a day or placebo for 3 years [53]. As expected, diabetes incidence was significantly decreased by 25% in the acarbose group (relative risk of 32.4% vs 41.5% in acarbose and placebo group, respectively), and acarbose significantly increased reversion to normal glucose tolerance \( P < 0.0001 \). Furthermore, the use of acarbose was associated with a statistically significant 49% decrease in the rate of any cardiovascular event, highlighting the cardiovascular protective effect of improving postprandial hyperglycemia with acarbose. This study had many limitations: a high percentage of participants discontinued treatment (31% in the acarbose group and 19% in the placebo group), most likely related to increased gastrointestinal adverse effects of acarbose. In addition, the diabetes prevention effect does not seem to be sustained: during a 3-month wash-out period where all patients received placebo, incidence of diabetes in the initial intervention group was higher than in the initial placebo group.

In a Japanese multicenter randomized double-blind trial, 1780 patients with IGT were randomly assigned to receive voglibose or placebo [54]. An interim analysis at 48 weeks revealed a significantly lower risk of progression to diabetes in the voglibose group. Nateglinide

Nateglinide is a short-acting insulin secretagogue that is mostly used in the treatment of postprandial hyperglycemia in diabetic patients. The protective effect of nateglinide in a prediabetic population was examined in the NAVIGATOR study (the NAteglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research), a large prospective multinational, randomized, double-blind, placebo-controlled trial. Nateglinide (30–60 mg 3 times daily) and valsartan (80–160 mg daily) versus placebo were used in a 2×2 factorial design in 9306 participants with IGT and increased risk of cardiovascular events [57]. At 5 years, nateglinide did not reduce the cumulative incidence of diabetes or cardiovascular outcomes, when compared to placebo, whereas risk of hypoglycemia was significantly increased in the intervention group.

**Liraglutide**

Liraglutide is an injectable glucagon-like peptide-1 (GLP-1) receptor agonist used to treat T2DM, and recently approved as a weight-reducing agent at the dose of 3 mg injected subcutaneously. GLP-1 receptor agonists work by stimulating insulin secretion in a glucose-dependent manner, suppressing glucagon secretion, inducing satiety, and slowing gastric emptying. In the international double-blind SCALE (Satiety and Clinical Adiposity-Liraglutide Evidence) trial, 3731 nondiabetic patients, among whom 61.2% had prediabetes, were randomly assigned to liraglutide 3 mg subcutaneous injection daily or placebo, in addition to diet and exercise [58]. Liraglutide was associated with lower glucose levels on OGTT and lower A1C values at the end of the study (56 weeks), with this decrease especially prominent in prediabetic
patients. Significantly fewer participants in the liraglutide group (4/2219) compared to the placebo group (14/1225) developed diabetes at 56 weeks, nearly all of whom (except for 1 in the placebo group) had prediabetes at the beginning of the study. Of note, the liraglutide group had a mean 8.4-kg weight reduction by week 56, compared to 2.8 kg in the placebo group.

**Insulin**

Insulin has also been investigated as a possible diabetes prevention agent, given the assumed protective effect insulin could exert on beta cell reserve. In the landmark international Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, 12,537 participants (mean age 63.5 years) with cardiovascular risk factors plus IFG, IGT, or type 2 diabetes were randomly assigned to receive insulin glargine (with a target FBG ≤ 95 mg/dL) or standard care and were monitored for cardiovascular outcomes and other secondary endpoints including incidence of diabetes [59]. After a median follow-up of 6.2 years, and 3 months after discontinuation of therapy, among the 1456 participants without baseline diabetes, new diabetes was diagnosed in 30% of participants receiving glargine versus 35% of those receiving standard therapy. However, rates of severe hypoglycemia and modest weight gain were higher in the insulin group, calling into question the benefit/risk balance with the use of basal insulin for diabetes prevention.

**ACE Inhibitors and ARBs**

A possible diabetes preventive effect was observed with renin-angiotensin system (RAS) blockade agents in secondary analysis of several hypertension trials, such as with ramipril in the Heart Outcomes Prevention Evaluation study, captopril (compared to diuretics and beta blockers) in the CAptopril Prevention Project, lisinopril (compared to amlodipine and chlorthalidone) in the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, losartan (compared to atenolol) in the Losartan Intervention For Endpoint reduction in hypertension study), and multiple other randomized controlled trials [60–64]. Therefore, 2 major trials were designed to examine, as a primary outcome, the effect of RAS inhibition on diabetes prevention in a population at risk. The DREAM trial randomly assigned, in a 2 x 2 factorial design, 5269 relatively healthy patients with IGT and/or IFG to rosiglitazone, ramipril, or placebo [65]. Although the use of ramipril at a dose of 15 mg daily for 3.5 years did not prevent diabetes significantly, it was associated with a 9%, nonsignificant decrease in new-onset of diabetes and a 16%, significant increase in regression of IFG and IGT to normoglycemia, as well as a significant decrease in OGTT 2-hour glucose level (135.1 vs 140.5 mg/dL) with no improvement in FBG.

Similarly, in the NAVIGATOR trial that examined the effect of nateglinide and valsartan on the prevention of diabetes in 9306 participants with IGT and increased risk of cardiovascular events, valsartan significantly but slightly reduced the incidence of diabetes at 5 years, by 14%, when compared to placebo (33% versus 37%, respectively), with no significant reduction in cardiovascular outcome [66]. Unlike in the DREAM study, the patients enrolled in the NAVIGATOR trial had established cardiovascular disease or cardiovascular risk factors and assumable elevated RAS activation level. This baseline population difference might explain the more significant effect of RAS inhibition in the NAVIGATOR trial.

Given the positive glycemic effect of ACE inhibitors and ARBs, their use should be encouraged in prediabetic patients when indicated for treatment of high blood pressure or cardiovascular disease. Different mechanisms could explain this favorable glycemic impact: inhibition of the post-receptor insulin signaling abnormalities, increased blood flow to the skeletal muscle facilitating insulin action, enhanced differentiation of pre-adipocytes into mature adipocytes, and increased pancreatic islet blood perfusion leading to appropriate insulin release and possible partial PPAR-γ activity [67].

**Xenical**

Xenical is a gastrointestinal lipase inhibitor approved for use for weight reduction and maintenance. A possible diabetes prevention benefit of xenical was initially suggested by a retrospective analysis of xenical treatment effects on obese patients with IGT [68]. This finding was subsequently confirmed by a multicenter randomized placebo-controlled study, XENical in the prevention of Diabetes in Obese Subjects (XENDOS), where 3305 obese subjects, with normal glucose tolerance or IGT were randomly assigned to either xenical 120 mg 3 times a day or placebo, in addition to lifestyle changes for all participants [69]. In the group of patients with IGT (694 subjects), xenical treatment was associated with a 45% risk reduction of progression to diabetes at 4 years (18.8% versus 28.8% in placebo), whereas participants
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with baseline normal glucose tolerance had no significant change in incidence of diabetes. On the other hand, weight reduction at 4 years was significantly greater in all patients who received xenical (5.8 kg in intervention group vs 3 kg in control group). The beneficial effect of xenical in diabetes prevention seems to be additive to the benefit of weight loss. As in many weight reduction trials, this study was limited by the high discontinuation rate in both groups (48% in xenical group and 66% in control group), probably related to insufficient clinical response.

Fibric Acid Derivatives (Bezafibrate)
Bezafibrate, a nonselective ligand/activator for PPAR-\(\alpha\), was found to reduce not only triglycerides, but also FPG, fructosamine, and A1C levels significantly in T2DM patients with hyperlipidemia [70]. Different mechanisms of glucose lowering have been suggested with bezafibrate: nonselective activation of PPAR-\(\gamma\), improving insulin sensitivity, and enhancing glucose disposal in adipose tissue and skeletal muscles [71]. Furthermore, bezafibrate treatment was associated with decreased incidence of diabetes in patients with IFG and in obese non-diabetic patients with normal glycemic levels [72,73]. In a posthoc analysis of the Bezafibrate Infarction Prevention study, 303 patients with IFG received either 400 mg of bezafibrate daily or placebo [73]. Over a mean follow-up of 6.2 years, development of diabetes was less prevalent (54.4% vs 42.3%, relative risk reduction of 22%) and delayed (mean 10 months) in the bezafibrate group compared to placebo. Multivariate analysis identified bezafibrate as an independent predictor of decreased risk of new diabetes development, regardless of BMI and lipid profile.

Surgery
Over the past decade, bariatric surgery has become one of the most effective interventions for inducing and sustaining weight reduction in severely obese patients, leading to a significant benefit in diabetes prevention or remission. The Swedish Obese Subject Study is a large ongoing prospective nonrandomized cohort study that between 1987 and 2001 enrolled 4047 nondiabetic obese participants who underwent gastric surgery or were matched obese control, with diabetes incidence measured at 2, 10 and 15 years [74–76]. At 15 years, analysis of the available cohort of the initial group showed that T2DM developed in 392 of 1658 control participants and in 110 of 1771 bariatric-surgery participants, corresponding to incidence rates of 28.4 and 6.8 cases per 1000 person-years, respectively (\(P < 0.001\)). The treatment effects on the incidence of T2DM were at least as strong after 2 years and 10 years of follow-up as after 15 years. This effect was most prominent among the 591 patients who had IFG at baseline, with a number needed to treat as low as 1.3. The surgery group maintained an average 20-kg weight loss at 15 years.

In another study of the effects of bariatric surgery, 150 of 152 obese participants with IGT who underwent gastric bypass achieved and maintained a normal glycemic profile at 14 years of follow-up [77]. Similarly, in a follow-up of 136 obese participants with IGT, 109 of whom underwent bariatric surgery, 1 participant in the surgical group developed diabetes, as compared with 6 out of 27 in the control group [78]. In a meta-analysis including studies involving 22,094 patients who underwent bariatric surgery, 76.8% had complete resolution of their diabetes [79]. The rapid improvement of glycemic profile after bariatric surgery is thought to be due to oral intake restriction as well as acute hormonal changes related to the exclusion of the upper gastrointestinal tract (eg, incretin and ghrelin levels variations) [80].

Conclusions and Recommendations
The natural history of T2DM allows identification of patients at risk for diabetes and implementation of prevention strategies, which seems to be a public health need given the alarming increase in diabetes incidence. Indeed, the onset of T2DM is typically preceded by many years of beta cell dysfunction translating into carbohydrate metabolism abnormalities such as IFG and IGT, providing an excellent window of opportunity to identify persons at risk and prevent progression to diabetes. Numerous randomized controlled trials established lifestyle modifications, including dietary changes, moderate weight loss, and moderate intensity physical activity, as safe and effective interventions to prevent diabetes. This protective effect has been consistently shown to be sustained for more than 10 years after the initial intervention. Pharmacologic agents such as metformin, thiazolidinediones, alpha-glucosidase inhibitors, xenical, liraglutide, and insulin have also been associated with diabetes prevention in patients at risk. However, except for metformin, safety concerns or lack of durable efficacy or tolerability seem to outweigh their potential diabetes prevention benefit.

Given their favorable glycemic effect, RAS blockade and fibrates should be considered, when indicated, as
reasonable treatment options for hypertension and hyperlipidemia in prediabetic patients. Bariatric surgery has been associated with a dramatic reduction in diabetes incidence in obese prediabetic patients and can be considered an alternative prevention measure in patients with severe obesity and prediabetes.

The recently updated ADA guidelines recommend referring patients with prediabetes to an intensive diet and physical activity behavioral counseling program; diet and activity goals should adhere to the tenets of the DPP, with a loss of 7% of body weight and at least 150 minutes of moderate physical activity (eg, brisk walking) per week [8]. Metformin therapy for diabetes prevention should be considered in patients with prediabetes, especially in those with BMI greater than 35 kg/m², those younger than 60 years of age, women with history of gestational diabetes, and/or those with rapidly rising A1C despite lifestyle modifications. Monitoring for development of diabetes, at least annually, and screening for and treatment of modifiable cardiovascular risk factors are suggested in patients with prediabetes [8].

Many lessons have been learned through the studies of diabetes prevention interventions. The challenge that remains is how to apply these interventions, especially the lifestyle modifications, in real world medical practice, at both the individual and public health level.

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