

# Type 2 Diabetes Prevention: A Review

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**T**ype 2 diabetes has increased dramatically in the past two decades, with 1.6 million cases diagnosed each year in the United States.<sup>1</sup> Diabetes prevalence is highest among the elderly and in certain ethnic groups, especially African Americans, Hispanic Americans, and Native Americans. People with diabetes have a two- to fourfold increased risk of developing cardiovascular disease, peripheral vascular disease, and stroke. These complications account for 65% of mortality from diabetes and, as of 2006, have made diabetes the seventh leading cause of death in the United States.<sup>1,2</sup>

Unfortunately, diabetes is often diagnosed relatively late in the course of the disease, at a point when many patients have already developed complications. In addition, management efforts are labor intensive and challenging for both patients and physicians. Furthermore, the economic burden associated with diabetes is substantial, with U.S. costs estimated at \$174 billion in 2007 and one of every five health care dollars spent on caring for someone diagnosed with diabetes.<sup>2</sup> The impact of diabetes on individuals' health and its economic burden to society have made its prevention a major goal of the current era.

In the past decade, major advances have been made in our understanding of the prevention of type 2 diabetes. Interventions that can reverse impaired glucose

regulation early in its course may be the key to primary prevention of the long-term complications of diabetes.

Type 2 diabetes is a heterogeneous disorder characterized by two interrelated metabolic defects: insulin resistance coupled with impaired insulin secretion by  $\beta$ -cells in the pancreas.<sup>3</sup> Therefore, strategies that target these two mechanisms by improving insulin sensitivity and protecting  $\beta$ -cell function have become the focus of prevention efforts. Weight loss and physical activity, as well as some medications, are thought to improve both insulin sensitivity and secretion. The results of major clinical diabetes prevention trials will be reviewed here.

## Lifestyle Modification

In the past decade, several randomized, controlled clinical trials have examined the role of diet and exercise in the prevention of type 2 diabetes.<sup>4</sup> One of the earliest studies was conducted in a Chinese community among 577 men and women with impaired glucose tolerance who were

randomized to a program of diet, exercise, or both.<sup>5</sup> Dietary intervention focused on increased amounts of vegetables and reduced consumption of alcohol and simple sugars; overweight individuals (those with a BMI > 25 kg/m<sup>2</sup>) were encouraged to lose weight. The exercise group was instructed to increase their daily activity by the equivalent of 20 minutes of moderate activity, such as brisk walking, and the diet-plus-exercise group was asked to do both exercise and dietary modification.

After 6 years of follow-up, all three interventions were similarly effective, with risk reductions of 31–46% compared to an untreated control group. During long-term follow-up of this cohort, most participants had progressed to diabetes, although diabetes prevalence was still lower in the former intervention groups (80% compared to 93% in the placebo group).<sup>6</sup>

More recently, the Finnish Diabetes Prevention Study (DPS)<sup>7</sup> randomized 522 overweight (average BMI 31 kg/m<sup>2</sup>) middle-aged individuals to either intensive lifestyle modification or a control group. The former entailed both specific dietary recommendations and exercise guidelines, including a weight-loss goal of 5% of total body weight and at least 30 minutes per day of combined aerobic activity and resistance training.

This study demonstrated a clinically significant impact of intensive lifestyle changes in the reduction of

## IN BRIEF

This review offers a discussion of various strategies for the prevention of type 2 diabetes. It includes results from recent clinical trials targeting patients who are at highest risk for the development of diabetes, with a particular emphasis on lifestyle modification strategies and the implementation of such programs in community-based settings.

diabetes. At the 3-year follow-up, the group reduced their cumulative risk by 58% compared to the control subjects. During the first year, the intervention group lost an average of 4.2 kg, which appeared to be the primary mediator of diabetes risk reduction. Further analysis demonstrated the impact of exercise on the risk reduction of diabetes: moderate to vigorous activity of at least 2.5 hours per week reduced the incidence of diabetes by 63–69%. In the extended follow-up (3 years after the active intervention was completed), the intensive lifestyle group maintained a 36% relative reduction in diabetes incidence, suggesting that these benefits could be maintained outside of a structured clinical trial setting.<sup>8</sup>

The largest clinical trial to date to study lifestyle intervention for the prevention of diabetes was the Diabetes Prevention Program (DPP).<sup>9</sup> The DPP randomized 3,234 overweight participants with impaired glucose tolerance and elevated fasting glucose from 22 sites in the United States to one of three interventions: intensive lifestyle intervention (ILS), metformin, or placebo. The participants were mostly middle aged and had an average BMI of 34 kg/m<sup>2</sup>. Forty-five percent were from ethnic and racial minority groups known to be at high risk for diabetes. The ILS group was instructed to follow a low-calorie, low-fat diet, with a weight-loss target of 7% of baseline body weight and an exercise goal of at least 150 minutes per week of moderate-intensity physical activity. The ILS group participated in a 16-week core curriculum focused on behavior modification, diet, and exercise education during the first 24 weeks, followed by at least monthly reinforcement.

After an average follow-up of 2.8 years, the ILS group achieved a

mean weight loss of 7%, and three-fourths of the participants met the exercise targets during the first 6 months of the study. The ILS group had a 58% reduction in the development of diabetes compared to the placebo group. Weight loss was the predominant predictor of reduced diabetes incidence, with a 16% reduction of developing diabetes for each kilogram of weight lost. However, participants who did not achieve their weight-loss targets but were able to achieve the exercise goal also benefited (44% risk reduction compared to placebo). The effectiveness of the ILS intervention was similar in men and women and among racial and ethnic groups. The greatest risk reduction was in participants older than 60 years of age, most likely because they achieved the biggest weight loss and the greatest increase in physical activity.<sup>10</sup>

After completion of the initial masked phase of the DPP, all participants were offered the ILS program in a group session format and then were enrolled in the DPP Outcome Study (DPPOS), which aimed to examine whether the diabetes prevention was sustainable over time. During DPPOS, all participants were provided with quarterly lifestyle sessions, and the original ILS subjects received additional group classes.

Results from an additional 6.8 years of follow-up in DPPOS were recently published.<sup>11</sup> After a median total follow-up of 10 years, the ILS group, which had initially lost ~7 kg in the first year of the DPP, weighed 2 kg less on average than at DPP randomization. During DPPOS, diabetes incidence rates in the metformin and former placebo groups fell to equal those in the former ILS group, but the cumulative incidence remained lowest in the ILS group

(34% risk reduction compared with placebo).

These results demonstrate that prevention or delay of diabetes achieved through lifestyle change can persist for at least 10 years. Furthermore, the decrease in diabetes incidence rates among former metformin and placebo groups suggests that lifestyle intervention provided in a group format is an effective approach.

Studies conducted in Japanese and Indian populations have also demonstrated the effectiveness of lifestyle modification in the prevention of diabetes.<sup>12,13</sup>

### **Bariatric Surgery**

Bariatric surgery as a means of achieving weight loss has proven to be successful in diabetes prevention. In one prospective trial of > 2,000 patients who underwent a variety of surgical procedures (most commonly, vertical banded gastroplasty) and a matched standard-care control group, the risk of diabetes in the surgical group was reduced by 86% at 2 years and 75% at 10 years of follow-up. None of those who lost at least 12% of their baseline weight developed diabetes, compared to 7% of those with 2% weight loss and 9% of those who gained weight.<sup>14,15</sup>

Bariatric surgery has also been reported to induce remission of existing diabetes. In a randomized, controlled trial of gastric banding versus conventional diet therapy, 73% of surgical patients achieved a remission compared to 13% of control subjects.<sup>16</sup> Gastric banding procedures improve glycemic control in patients with established diabetes, further supporting the potential benefit in diabetes prevention for appropriately selected patients.<sup>17</sup>

### **Pharmacological Agents**

Although moderate-intensity exercise and weight loss clearly have been

shown to be effective in reducing diabetes risk, not all patients are able to achieve these lifestyle goals. For these patients and those who progress despite successful weight loss, additional therapeutic options are needed. Several pharmacological agents have been studied in clinical diabetes prevention trials.

### Metformin

Metformin is the most widely studied drug for diabetes prevention. In the DPP, participants randomized to metformin (850 mg, twice daily) achieved a 31% reduction in diabetes compared to placebo.<sup>9</sup> Metformin was most effective in more obese participants (baseline BMI > 35 kg/m<sup>2</sup>), who experienced a 53% reduction of diabetes incidence, and in participants < 45 years of age, who saw a 44% reduction. Metformin had little benefit for older individuals who were 60–85 years of age at baseline. The effectiveness of metformin was attributed in part to weight loss, which averaged 1.7 kg and accounted for 64% of the beneficial effect of metformin.<sup>9</sup> Importantly, after an average of 10 years of follow-up, the metformin group had maintained an average weight loss of 2.5 kg, and diabetes risk was reduced by 18% compared to the former placebo group.<sup>11</sup> Smaller studies conducted in India and China reported similar reductions in diabetes risk.<sup>13,18</sup>

In general, metformin is widely available, inexpensive, and relatively well tolerated. These studies suggest that this medication is an appropriate treatment approach in appropriately selected patients, especially those who are younger and overweight.

### Acarbose

The  $\alpha$ -glucosidase inhibitor acarbose was studied in the Study to Prevent Non-Insulin-Dependent Diabetes (STOP-NIDDM) trial, which ran-

domized 1,429 participants with impaired glucose tolerance to either acarbose, 100 mg, or placebo three times daily for a mean of 3.3 years.<sup>19</sup> In this study, subjects in the acarbose treatment arm had a 25% reduction in the incidence of diabetes. However, almost one-third of the acarbose group was unable to complete the study because of gastrointestinal side effects, which makes the results of the study difficult to interpret and the applicability to clinical care unclear.

### Thiazolidinediones

The thiazolidinediones (TZDs) have also been studied as potential agents for diabetes prevention. In the first year of the DPP, diabetes incidence was reduced by 75% in the troglitazone arm before it was discontinued because of evidence of hepatotoxicity.<sup>20</sup> Troglitazone was also studied in a cohort of women with recent gestational diabetes and reduced diabetes by ~50% compared to untreated controls.<sup>21</sup> Rosiglitazone was studied in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial,<sup>22</sup> a large, international study that randomized high-risk patients (impaired fasting glucose, impaired glucose tolerance, or both) to rosiglitazone, 8 mg daily, or placebo. After an average follow-up of 3 years, the incidence of diabetes in the rosiglitazone group was reduced by 62% compared to placebo. Glucose intolerance was normalized in 50% of the rosiglitazone group compared to only 30% in the placebo group.

However, rosiglitazone does have well-known side effects, such as weight gain and peripheral edema; in the DREAM trial, the TZD group gained 2.2 kg more weight than the placebo group. Additional concerns include the controversy surrounding the potential cardiotoxicity of rosiglitazone and a report of increased fractures in women taking this medication, both of which have

diminished enthusiasm for its routine use in diabetes prevention.<sup>23,24</sup>

### Vascular Outcomes

Although delay of the diagnosis of diabetes is the primary outcome in all diabetes prevention studies, the critical clinical issue is the prevention of the micro- and macrovascular complications of diabetes. Indeed, these complications account for the morbidity and mortality of the disease, and the ultimate goal of diabetes prevention is to avoid these devastating outcomes.

Investigators from the STOP-NIDDM trial reported a 49% reduction in cardiovascular events in the acarbose-treated group during the 3.3 years of follow-up, but the number of events was small, and this finding remains to be confirmed.<sup>25</sup> Cardiovascular disease risk markers were improved in the ILS group in the DPP, including lipoproteins, C-reactive protein, and fibrinogen.<sup>26</sup> During long-term follow-up, this group continued to show improvements in both lipids and blood pressure measurements, despite the fact that they were receiving less drug treatment for these conditions.<sup>11</sup> Longer-term follow-up of the DPP cohort may provide more definitive data on cardiovascular and microvascular outcomes.

### Translation and Cost-Effectiveness of Diabetes Prevention

The protocols employed in most lifestyle intervention trials are labor intensive and require dedicated staff and resources, raising issues about the economics of implementing these programs. Analyses of the costs of various strategies are conflicting, and two fundamental questions have emerged. First, if we elect to treat prediabetes, which of the strategies is the most cost-effective? Second, is it more economically prudent to start such a program in patients who are at high

risk for diabetes, or should treatment be initiated only after diabetes has developed?

The DPP investigators analyzed the cost per quality-adjusted life year (QALY), comparing the lifestyle and metformin interventions to placebo.<sup>27</sup> The cost per QALY for the ILS intervention was ~\$1,100 compared to \$31,300 for the metformin intervention. This led investigators to conclude that, compared to placebo, the ILS intervention was not only the most effective treatment for diabetes prevention, but also the most cost-efficient. Furthermore, when compared to other well-accepted interventions, they concluded that both DPP interventions would be cost-effective from societal and health system perspectives.

However, another analysis concluded that such programs are too expensive for widespread implementation and suggested that it may be preferable to delay intervention until diabetes is diagnosed.<sup>28</sup> Much of the discrepancy between these analyses derives from varying assumptions about rates of progression to diabetes and its complications and differences in analytic approach. However, cost-benefit analyses have been reported from other diabetes

prevention trials with generally favorable results.<sup>29,30</sup>

Lifestyle intervention has been conclusively proven effective in reducing diabetes risk, but for such an approach to be broadly implemented, it must be translated into community-based settings that are both accessible and affordable. Although such translation efforts are in their infancy, a number of significant efforts have been initiated (Table 1).

Finnish investigators have developed a community-based model for intensive lifestyle intervention called Good Ageing in Lahti (GOAL).<sup>31</sup> This program identified high-risk participants from Finnish primary care settings and enrolled them in six 2-hour group counseling sessions that were based on a social-cognitive health behavior model and led by public health nurses.<sup>32,33</sup> Although the results of the GOAL trial were not as robust as the DPS in terms of meeting weight-loss and physical-activity targets (12 versus 43% and 65 versus 86%, respectively), this primary care-based program demonstrated a significant reduction in weight and BMI in high-risk individuals. Of the participants who had impaired glucose tolerance at baseline, 12% went on to develop type 2 diabetes at 3 years,

and 43% returned to normal glucose tolerance.

Marrero and Ackermann developed a community-based program closely modeled after the DPP ILS for implementation at local YMCAs.<sup>34</sup> This program included a three-step approach: a 16-week core curriculum, a 4-week “training and refinement” phase, and a long-term maintenance phase. The core curriculum included weekly small-group sessions focused on mapping out explicit exercise plans and building problem-solving skills. In the second phase, participants met twice weekly with either a training partner or as a group to exercise. In the maintenance phase, monthly meetings included participants and their family members and addressed common barriers to weight loss and exercise (e.g., holidays and restaurant meals) and used many of the same tools as the original DPP.

High-risk individuals randomized to the group lifestyle program achieved a mean weight loss of 6% compared to only a 2% weight loss in a control group, which was sustained at 12 months.<sup>35</sup> Furthermore, the intervention group had a significantly reduced estimated 10-year risk of coronary heart disease (based on blood pressure, lipid levels, and A1C), supporting the potential for this community-based program to

**Table 1. Resources for Implementing Lifestyle Modification**

For Professionals	For Patients
<ul style="list-style-type: none"> <li>• DPP Lifestyle Program, <a href="http://www.bsc.gwu.edu/dpp/manuals.htmlvdoc">http://www.bsc.gwu.edu/dpp/manuals.htmlvdoc</a> <ul style="list-style-type: none"> <li>○ Includes lifestyle manuals for Core (sessions 1–16) and Beyond Core for implementing the ILS program</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• National Diabetes Education Program, <a href="http://www.ndep.nih.gov/">http://www.ndep.nih.gov/</a> <ul style="list-style-type: none"> <li>○ Includes the “Game Plan” package of risk assessment, fat and calorie counter, and a food and activity tracker</li> <li>○ Tips on preventing diabetes</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• GOAL Program, <a href="http://www.palmenia.helsinki.fi/ikihyva/InEnglish.html">http://www.palmenia.helsinki.fi/ikihyva/InEnglish.html</a> <ul style="list-style-type: none"> <li>○ Guide for implementing the Finnish GOAL community-based ILS program</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• American Diabetes Association, <a href="http://www.diabetes.org/diabetes-basics/prevention/">http://www.diabetes.org/diabetes-basics/prevention/</a> <ul style="list-style-type: none"> <li>○ Prevention resources</li> </ul> </li> </ul>

delay or prevent not only the onset of diabetes, but also the associated cardiovascular complications.<sup>36</sup> The cost per person to implement this type of community lifestyle intervention program was estimated at between \$275 and \$325 annually compared to the original DPP ILS intervention cost of \$1,400 per participant for the first year.<sup>37,38</sup> This provides strong evidence that dissemination of the DPP lifestyle intervention in a well-established community organization is feasible and can be cost-effective.

There are similar group-based lifestyle intervention programs underway in communities throughout the United States. A recent review examined several such programs that were implemented in a wide variety of environments, including a rural Southern church community and an inner-city urban population in the Northeast.<sup>39</sup> Although the programs varied in length and target population, all reported significant weight loss and increased physical activity.

One of the larger translation efforts was reported by the Montana Diabetes Control Program, which collaborated with four health care facilities (urban and rural) to implement a group-based lifestyle program based on the DPP. This effort produced weight-loss results comparable to the DPP (mean weight loss 6.7 kg at 6 months), and most participants also achieved physical-activity goals.<sup>40</sup>

Such results reinforce the feasibility of effective community-based lifestyle intervention strategies for diabetes prevention in diverse populations and in varied settings. However, much remains to be done to gain commitment from insurers and health care systems to ensure

**Table 2. Recommendations for Screening for Pre-Diabetes and Diabetes<sup>41</sup>**

1. Testing should be considered in all adults who are overweight (BMI  $\geq$  25 kg/m<sup>2</sup>) and have additional risk factors:
  - physical inactivity
  - first-degree relative with diabetes
  - members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
  - women who delivered a baby weighing > 9 lb or were diagnosed with gestational diabetes mellitus
  - hypertension ( $\leq$  140/90 mmHg or on therapy for hypertension)
  - HDL cholesterol level < 35 mg/dl and/or a triglyceride level > 250 mg/dl
  - women with polycystic ovarian syndrome
  - A1C  $\leq$  5.7%, impaired glucose tolerance or impaired fasting glucose on previous testing
  - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
  - history of cardiovascular disease
2. In the absence of the above criteria, testing for pre-diabetes and diabetes should begin at the age of 45 years.
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

broad implementation for high-risk populations.

**Who Should Be Targeted for Diabetes Prevention?**

The first step in diabetes prevention is identifying patients who are at highest risk. This group includes individuals of any age who are overweight and obese (BMI  $\geq$  25 kg/m<sup>2</sup>) with at least one risk factor (such as high-risk ethnic group, first-degree relative with diabetes, personal history of gestational diabetes, or sedentary lifestyle). The American Diabetes Association (ADA) recommends that these patients should be screened every 3 years (Table 2). All other patients should begin screening at the age of 45 years.<sup>41</sup>

The laboratory diagnosis of “at risk” has traditionally been determined by the presence of impaired fasting glucose or impaired glucose tolerance. However, the current ADA clinical practice recommendations recommend that A1C

measurement may be used as a screening tool, with levels between 5.7 and 6.4% defining those at highest risk for diabetes.<sup>41</sup> This simple blood test is readily available in most primary care settings, can be performed regardless of fasting status, and has the potential to more easily identify patients who would benefit from diabetes prevention measures. Validation of this approach remains to be completed, however.

**Conclusions**

Recent clinical trials have convincingly shown that lifestyle modification is the most effective tool in the prevention or delay of type 2 diabetes. For overweight and obese patients, a modest weight-loss goal of 5–10% (often < 20 lb) can substantially reduce the risk of diabetes. Moderate-intensity physical activity such as brisk walking for at least 150 minutes per week also plays an important role in reducing diabetes risk, even in the absence of weight loss (Table 3).

**Table 3. Recommendations and Resources for Lifestyle Modification for Diabetes Prevention**

**General Recommendations for Lifestyle Modification for the Prevention of Diabetes**

- Moderate-level physical activity (e.g., brisk walking) for at least 30 minutes per day, 5 days per week
- Weight-loss goals of 5–15% of starting weight, with target 1–2 lb weekly
- Limit fat content to < 30 % of total daily calories
- Reduce portion sizes and daily caloric intake
- Increase fruits, vegetables, and fiber in diet

For patients who are unable to achieve these lifestyle goals or those who progress despite exercising and losing weight, metformin has also been proven effective, especially in younger obese patients. Acarbose, when tolerated at the maximum effective dose, may also confer a moderate risk reduction. Data regarding thiazolidinediones are conflicting, and the reports of cardiovascular and fracture risk make this option less attractive as a prevention strategy. However, none of these medications are as robust in diabetes prevention as the lifestyle intervention strategies, and cost-effectiveness analyses suggest that pharmacotherapy may have greater financial costs.

Perhaps the most pressing clinical question remaining is whether these prevention strategies will reduce the vascular complications of diabetes that are the cause of the greatest financial burden and personal suffering in patients with diabetes. Prevention of diabetes is our most powerful intervention, and successful implementation of these proven strategies should be the focus of our efforts.

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