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## The Diabetes Prevention Program and Its Global Implications

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### Abstract

Type 2 diabetes affects over 150 million adults worldwide and this figure is expected to double over the next 25 yr. This increase will be accompanied by a marked increase in the number of patients with ESRD due to diabetes. We hypothesized that a lifestyle-intervention program or the administration of metformin would prevent or delay the development of diabetes. We randomly assigned 3234 nondiabetic persons with elevated fasting and post-load plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of at least a 7% weight loss and at least 150 min of physical activity per week. The mean age of the participants was 51 yr, and the mean body mass index was 34.0 kg/m<sup>2</sup>; 68% were women, and 45% were members of non-Caucasian racial/ethnic groups. The average follow-up was 2.8 yr. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced the incidence of diabetes by 58% (95% CI: 48 to 66%) and metformin by 31% (95% CI: 17 to 43%), compared with placebo; the lifestyle intervention was significantly more effective than metformin. In conclusion, lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk and the lifestyle intervention was more effective than metformin. Because the lifestyle changes worked equally in all racial/ethnic groups in the Diabetes Prevention Program, they should be applicable to high-risk populations worldwide and may be able to reduce the projected progressive rise in the incidence of diabetes and the expected increase in ESRD.

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Type 2 diabetes mellitus is a serious disease affecting approximately 4.0% of adults in the world in 1995 (1) and this prevalence has been projected to rise to 5.4% by 2025 (2). This increase is occurring to a disproportionate extent in the developing countries, especially those of Asia (2,3). The worldwide increase in the prevalence of diabetes has been accompanied by a three- to fourfold increase in the incidence of ESRD, making diabetes the single leading cause of ESRD in most countries (4). Although treatment of diabetes can prevent some complications

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(5,6), it does not usually restore normoglycemia or eliminate nephropathy and the other long-term complications of diabetes. Prevention of diabetes is clearly preferable (7,8).

Obesity adds to the inherent insulin resistance of type 2 diabetes, as does lack of exercise (reviewed in 9), leading to the concept that weight loss and increased activity levels may be effective in preventing diabetes in susceptible individuals. A number of observational studies have shown that the development of diabetes is associated with increasing weight and weight gain, and is reduced with exercise (10,11), supporting this concept.

The Diabetes Prevention Program (DPP) Research Group conducted a large, prospective, randomized clinical trial involving adults in the United States who were at high risk for the development of type 2 diabetes (12,13). The study was designed to answer the following question: Does a lifestyle intervention or treatment with metformin prevent or delay the onset of diabetes?

## Materials and Methods

Twenty-seven centers participated in the DPP. The methods have been described in detail elsewhere (12). Eligibility criteria included age  $\geq 25$  yr, body mass index of  $\geq 24$  kg/m<sup>2</sup> or higher ( $\geq 22$  in Asians), and a fasting plasma glucose concentration of 95 to 125 mg/dl (5.3 to 6.9 mmol/L) ( $\leq 125$  mg/dl in the American Indian clinics) and 140 to 199 mg/dl (7.8 to 11.0 mmol/L) 2 h after a 75-g oral glucose load, *i.e.*, impaired glucose tolerance (IGT) with elevated fasting glucose levels.

Participants were randomly assigned to one of three interventions: metformin 850 mg twice daily, placebo twice daily, or an intensive program of lifestyle modification. The study initially included a fourth intervention, troglitazone, which was discontinued in 1998 because of the drug's potential liver toxicity (12,13). In the intensive lifestyle arm, the goals were to achieve and maintain a weight reduction of at least 7% of initial body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 min/wk. A curriculum covering diet, exercise, and behavior modification was taught in both one-to-one and group sessions (12).

The primary outcome was the development of diabetes, diagnosed on the basis of an annual oral glucose-tolerance test (OGTT) or a semiannual fasting plasma glucose test, according to the 1997 criteria of the American Diabetes Association: fasting plasma glucose  $\geq 126$  mg/dl (7.0 mmol/L) or  $\geq 200$  mg/dl (11.1 mmol/L) 2 h after a 75-g oral glucose load (14). The diagnosis required confirmation by a second OGTT within 6 wk (12).

Assignments to metformin and placebo were double-blinded. The study design and analysis followed the intention-to-treat principle. The blinded treatment phase was terminated 1 yr early, in May 2001, on the basis of data obtained through March 31, 2001, the closing date for this report. Details of the statistical analyses used have been reported previously (13).

## Results

Between 1996 and 1999, 3234 study participants were randomly assigned to one of the three interventions (1082 to placebo, 1073 to metformin, and 1079 to the intensive lifestyle intervention). The three groups had similar baseline characteristics, including all measured risk factors for diabetes (15). The mean duration of follow-up was 2.8 yr (range, 1.8 to 4.6).

The goal of weight loss of  $\geq 7\%$  was achieved by 50% of the participants in the lifestyle-intervention group by the end of the core curriculum (at 24 wk), and 38% had a weight loss of at least 7% at the time of the most recent visit. The percentage of subjects in the lifestyle-

intervention group who met the weekly goal of at least 150 min of physical activity was 74% at 24 wk and 58% at the most recent visit. Dietary change was assessed only at 1 yr. Daily energy intake decreased by a mean ( $\pm$  SEM) of  $249 \pm 27$  kcal in the placebo group,  $296 \pm 23$  kcal in the metformin group, and  $450 \pm 26$  kcal in the lifestyle-intervention group ( $P < 0.001$ ). Average fat intake, which was 34.1% of total calories at baseline, decreased by  $0.8 \pm 0.2\%$  in the placebo and metformin groups and by  $6.6 \pm 0.2\%$  in the lifestyle-intervention group ( $P < 0.001$ ). The percentage of participants who took at least 80% of the prescribed dose of the study medication was slightly higher in the placebo group than in the metformin group (77% versus 72%,  $P < 0.001$ ). Ninety-seven percent of the participants taking placebo and 84% of those taking metformin were given the full dose of one tablet (850 mg in the case of metformin) twice a day; the remainder were given one tablet a day to limit side-effects.

Changes in weight and leisure physical activity in all three groups are shown in Figure 1. Participants in the lifestyle intervention cohort had much greater weight loss and a greater increase in leisure physical activity than did participants in the metformin or placebo cohorts. The average weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle-intervention groups, respectively ( $P < 0.001$ ).

The cumulative incidence of diabetes was significantly lower in the metformin and lifestyle-intervention groups than in the placebo group throughout the follow-up period (Figure 2), the crude incidence rates being 11.0, 7.8, and 4.8 cases per 100 person-years for the placebo, metformin, and lifestyle-intervention groups, respectively. The incidence of diabetes was 58% lower (95% CI: 48 to 66%) in the lifestyle-intervention group and 31% lower (95% CI: 17 to 43%) in the metformin group than in the placebo group. The results of all three pairwise group comparisons were statistically significant by the group-sequential log-rank test. None of these results were substantially affected by adjustment for baseline characteristics. The estimated cumulative incidence of diabetes at 3 yr was 28.9%, 21.7%, and 14.4% in the placebo, metformin, and lifestyle-intervention groups, respectively. On the basis of these rates, the estimated number of persons who would need to be treated for 3 yr to prevent one case of diabetes during this period is 6.9 (95% CI: 5.4 to 9.5) for the lifestyle intervention and 13.9 (95% CI: 8.7 to 33.9) for metformin.

Treatment effects did not differ significantly according either to gender or to race or ethnic group. The lifestyle intervention was highly effective in all subgroups. The effect of metformin was less with a lower body mass index ( $<30$  kg/m<sup>2</sup>) and age over 60 yr. Thus, the advantage of the lifestyle intervention over metformin was greater in older persons or those with a lower body mass index than in younger persons or those with a higher body mass index.

The rate of gastrointestinal symptoms was highest in the metformin group, and the rate of musculoskeletal symptoms was highest in the lifestyle-intervention group. Hospitalization and mortality rates were unrelated to treatment. No deaths were attributed to the study interventions.

## Discussion

The results from this study show that diabetes can be prevented or delayed in a substantial proportion of those at high risk for the disease (13). The incidence of diabetes was reduced by 58% with the lifestyle intervention and by 31% with metformin, compared with placebo. These effects were similar in men and women, and in all racial and ethnic groups. The intensive lifestyle intervention was as effective in older participants as it was in younger participants. The risk reduction we found with lifestyle intervention was the same as that found in a similar study conducted in Finland (16), and was higher than the reductions associated with diet (31%), exercise (46%), and diet plus exercise (42%) in a study in China (17). Our study, however, was

not designed to test the separate contributions of dietary changes, increased physical activity, and weight loss on the reduction in the risk of diabetes.

The incidence of diabetes in the placebo group (11.0 cases per 100 person-years) was higher than anticipated (12) and higher than seen in observational studies (10). The incidence rates of diabetes were similar among racial and ethnic groups despite differences in these subgroups in observational population-based studies (1,10). Racial- and ethnic-group differences in the incidence of diabetes were presumably reduced in our study by the selection of persons who were overweight, and had elevated fasting and postload glucose concentrations— three of the strongest risk factors for diabetes.

Drugs used to treat diabetes had not previously been shown to be effective for its prevention, perhaps because of small sample size and other methodological differences (7). However, in this study, metformin was effective, although less so than the lifestyle intervention. Metformin was less effective in persons with a lower baseline body mass index or a lower fasting plasma glucose concentration than in those with higher values for these variables. These findings are consistent with the observation that metformin suppresses endogenous glucose production, the main determinant of fasting plasma glucose concentrations (9).

In the United States the prevalence of IGT is modestly greater than that for diabetes (diagnosed and undiagnosed) (15.6% *versus* 12.3%), according to data from the Third National Health and Nutrition Examination Survey (1). If this is extrapolated to the entire world, where it is estimated that in the year 2000 there were approximately 155 million people with diabetes, the prevalence of IGT can be estimated to have been 197 million people (2). Furthermore, with the estimated projection of the prevalence of diabetes in the year 2025 of 300 million people (2), it can be estimated that 380 million people will have IGT. In areas of Asia and other previously underdeveloped areas, it is thought that this increasing prevalence of glucose intolerance is reflective of improvements in nutrition, hygiene, control of infectious diseases, and overall access to better medical care with increases in life expectancy along with decreased exercise associated with urbanization (2,3).

The fact that the benefits of weight loss and exercise were effective across all racial/ethnic groups, including African Americans and Asian Americans, in the DPP has important implications for the world population for diabetes in general and diabetic nephropathy in particular. The incidence of patients with diabetic ESRD increased approximately threefold between the 1980s and 1990s in various countries around the world (4). Where the two types of diabetes have been studied separately, it has been found that the total numbers with type 1 diabetes with ESRD have remained relatively constant but that there has been an extraordinary increase in the number of patients with type 2 diabetes with ESRD (4). At present, in most programs caring for patients with ESRD around the world, there are more patients with type 2 diabetes than those with type 1 (4).

The increasing number of patients with type 2 diabetes having nephropathy worldwide is, in part, related to the fact that those of non-Caucasian racial origin with type 2 diabetes have higher risks for diabetic nephropathy. It is known from studies in the United States and other countries that blacks, Asians, Latinos, and Native Americans have increased risks for development of diabetic nephropathy (18,19) and that this is not due solely to differential access to health care. For example, in a recent study of patients receiving relatively uniform clinical care in a managed care program in California, the adjusted hazard ratios for the development of nephropathy, compared with Caucasians, were 2.03, 1.85, and 1.45 for blacks, Asians, and Latinos, respectively (20). However, most of the increase is due to the rapid increase in the number of individuals developing diabetes along with their overall improvement in longevity (4).

Once diabetes develops, glycemic control and BP control are important means of delaying and possibly preventing the development and progression of nephropathy (5,6,21,22). Subsequently, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers appear to have selective further benefit in decreasing the rate of progression of established nephropathy (23). Although these aspects of care for more advanced stages of disease are thought to be cost effective (24,25), it clearly would be advantageous to prevent the disease altogether, or delay it as long as possible.

If the modest lifestyle interventions of 5 to 7% weight loss and increased activity of 150 min/wk shown to be effective in the DPP and other studies (15,16) were implemented in all susceptible populations, there would be a substantial reduction in the incidence of diabetes worldwide. The fact that the DPP interventions were equally effective across all racial/ethnic groups suggests that this approach to prevention of diabetes would be expected to ultimately reduce both the prevalence of diabetes and the prevalence of ESRD due to diabetes. Community-based programs that could be instituted at low cost to increase physical activity and help in weight loss have been advocated in this regard by the American Diabetes Association and the National Institutes of Health (8). Ultimately, the benefits would depend on whether glucose concentrations could be maintained at levels below those that are diagnostic of diabetes and whether the maintenance of these lower levels improve long-term outcomes. In addition, weight loss and exercise may also have independent effects in reducing cardiovascular disease (26).

In summary, the DPP showed that treatment with metformin and modification of lifestyle were two highly effective means of delaying or preventing type 2 diabetes. The lifestyle intervention was particularly effective, with one case of diabetes prevented per seven persons treated for 3 yr. Thus, it should also be possible to delay or prevent the development of diabetic nephropathy and other complications, substantially reducing the individual and public health burden of diabetes. A longer-term follow-up study of the DPP cohort is currently underway to help answer these questions.

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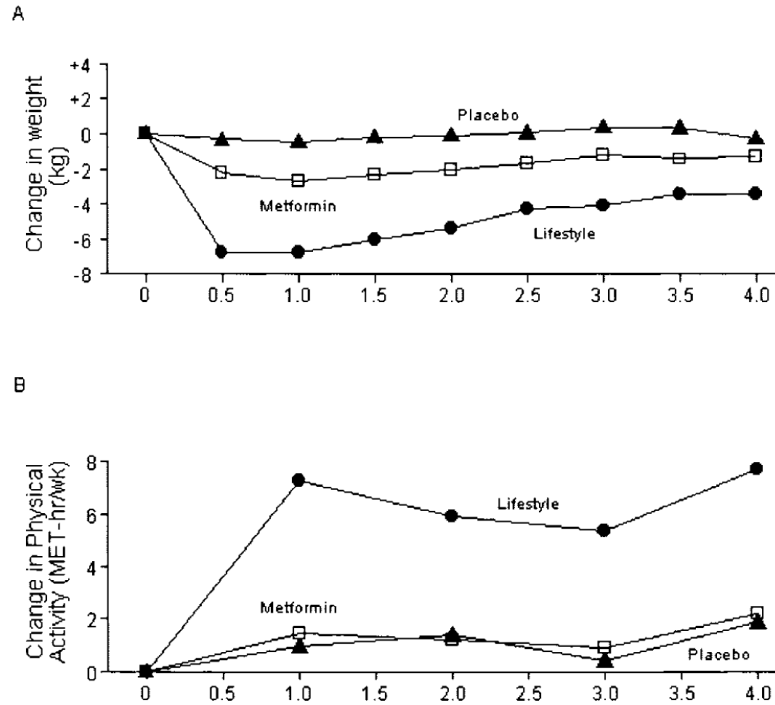
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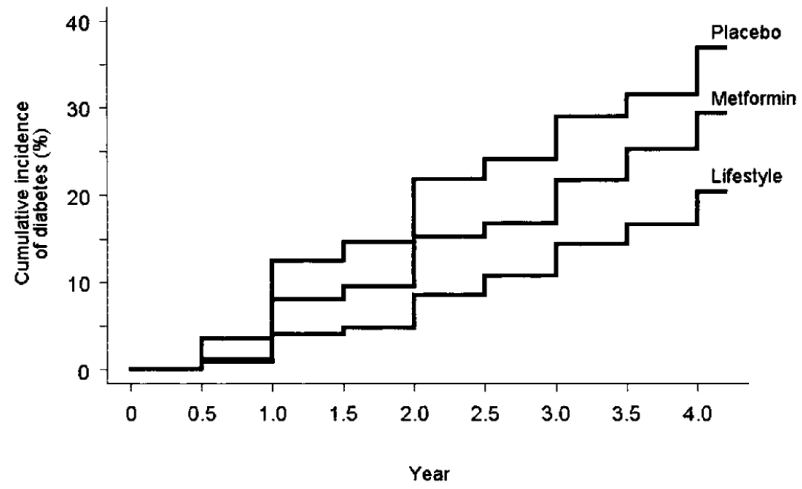
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**Figure 1.** Changes in (A) body weight and (B) leisure physical activity according to study group. Each data point represents the mean value for all participants examined at that time. The number of participants decreased over time because of the variable length of time that persons were in the study. For example, data on weight were available for 3085 persons at 0.5 yr, 3064 at 1 yr, 2887 at 2 yr, and 1510 at 3 yr. Changes in weight and leisure physical activity over time differed significantly among the treatment groups ( $P < 0.001$  for each comparison).





**Figure 2.** Cumulative incidence of diabetes according to study group. The incidence of diabetes differed significantly among the three groups ( $P < 0.001$  for each comparison).