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AN UPDATE ON THE DIABETES PREVENTION PROGRAM

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Abstract

Objective—To summarize the results of the Diabetes Prevention Program (DPP) and describe the additional 5-year follow-up study.

Methods—The design, implementation, and outcome of the DPP are reviewed, and an economic analysis of the effects of diabetes prevention and delay is presented.

Results—The DPP, thus far the largest diabetes prevention trial with the most ethnically diverse patient population, originally consisted of more than 3,800 subjects with impaired glucose tolerance. These subjects were randomized to receive one of four interventions: intensive lifestyle adjustments or standard lifestyle plus one of the following—placebo, metformin, or troglitazone. In June 1998, the troglitazone treatment was discontinued after a fatal case of liver failure in a study participant, but the subjects in this arm of the study continued to undergo follow-up. Thus, 3,234 subjects remained in the other three arms of the study. After a mean of 2.8 years of follow-up, the DPP was prematurely terminated because of an observed significant benefit to the intervention groups. Both metformin therapy and intensive lifestyle intervention reduced the risk of developing diabetes (by 31% and 58%, respectively, in comparison with placebo), and both interventions were deemed to be cost-effective on the basis of computer projections over a lifetime. Because of the premature discontinuation of the DPP, the durability of the interventions on diabetes prevention and the effect on microvascular and macrovascular disease could not be assessed. The subsequent outcomes study will address these issues during a 5-year follow-up period.

Conclusion—The DPP showed that both metformin and intensive lifestyle modifications effectively delayed or prevented the development of diabetes in a cost-effective manner.

Abbreviations

BMI = body mass index; CVD = cardiovascular disease; DPP = Diabetes Prevention Program; DPP-OS = Diabetes Prevention Program Outcomes Study; IGT = impaired glucose tolerance; QALY = quality-adjusted life-years

INTRODUCTION

The Diabetes Prevention Program (DPP) was a National Institutes of Health-sponsored, multicentered, clinical trial conducted in 27 clinical centers throughout the United States, with recruitment initiated in July 1996. The DPP is the largest diabetes prevention trial, including the most diverse patient population and multiple therapeutic interventions, yet to be published. More than 3,800 subjects with impaired glucose tolerance (IGT) were randomized into the original four-arm trial. Subjects were initially randomized to receive either an intensive lifestyle intervention or standard lifestyle intervention plus one of the following: placebo, metformin (850 mg twice a day), or troglitazone (400 mg daily) (1). On June 4, 1998, troglitazone treatment was discontinued in the DPP trial after a fatal episode of liver failure in

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a DPP participant. At that time, subjects receiving troglitazone were unblinded to their therapy, were offered group lifestyle classes of an intensity less than that received in the intensive lifestyle intervention group, and continued to undergo follow-up according to the DPP schedule of events. Thus, 3,234 subjects remained randomized among the other three arms of the study. The initial publications from the DPP were limited to this cohort of 3,234 participants in the three-arm study.

THREE-ARM STUDY RESULTS

The goal of enrollment into the DPP was to include a broad spectrum of the American population, with over-recruitment of those ethnic groups disproportionately affected by diabetes. Ethnic stratification of those enrolled in the three-arm study included 55% white subjects, 20% African American, 16% Hispanic American, 5% American Indian, and 4% Asian Pacific Islanders. Of the study participants, 68% were women, and the age distribution ranged from 25 to 87 years, with 20% older than age 60 years (2,3).

After a mean of 2.8 years of follow-up, with a maximum of almost 5 years of follow-up in the first study subjects randomized, the DPP was prematurely terminated by the National Institute of Diabetes and Digestive and Kidney Diseases on the advice of the Data Safety Monitoring Board because of an observed significant benefit to the intervention groups. End of study visits and data lock were quickly initiated, and subjects were unmasked to their treatment assignments.

Compliance with the treatment interventions was high throughout the DPP. Medication compliance with placebo and metformin did not differ and approximated 80%. A clear-cut differential response in physical activity and weight loss was noted among the three treatment groups, with physical activity remaining unchanged in the placebo and metformin groups, whereas those in the lifestyle intervention group (4) increased their metabolic-equivalent hours per week by approximately 7 within the first year and maintained that increase for the duration of the study. The study subjects in the intensive lifestyle group succeeded in reaching their target goal of a 7% mean weight loss by 6 months and were able to maintain that level of mean weight loss for the first 12 months (5). Subsequently, they underwent a slow weight regain, and they had a mean weight loss of 4% at the time of study termination. The placebo group maintained their weight throughout the duration of the study, with neither weight gain nor weight loss, whereas the metformin treatment group initially lost a mean of approximately 2.5% of their body weight within the first year and then regained weight during the subsequent 2 years.

The primary outcome of the DPP—the effect of the intervention strategies on the development of diabetes—is reflected in Table 1. The population of subjects with IGT and an elevated fasting plasma glucose level demonstrated an exceptionally high rate of progression to confirmed diabetes mellitus. Those study participants in the placebo group reflect the natural history of progression of IGT to diabetes and demonstrated an 11% per year incidence. This rate was reduced by 31% (to 7.8% per year) by treatment with metformin and by 58% (to 4.8% per year) by intensive lifestyle intervention.

Of particular note, study subjects from ethnic groups disproportionately affected by diabetes showed no difference in rates of progression to diabetes among the placebo cohort in comparison with white subjects in the DPP. This finding suggests that ethnic minority populations are at higher risk for the development of IGT but that further progression to diabetes may be independent of ethnic risk. Nonetheless, all ethnic populations seem to respond to the same degree to either metformin treatment or intensive lifestyle intervention.

This result was not the case, however, when the study population was stratified by either age or levels of obesity. Although the subjects in the placebo group progressed to diabetes independent of age or time of randomization, metformin therapy did not differ from placebo among the strata of participants older than age 60 years at study initiation. At the opposite extreme, those study participants between the ages of 25 and 44 years at study initiation responded equally to either metformin or intensive lifestyle, with an approximate 50% reduction in the development of diabetes. Similarly, when the study population was stratified by body mass index (BMI) at study initiation, metformin was ineffective at preventing the development of diabetes among those subjects with a BMI between 24 and 30 kg/m² but was equivalent to intensive lifestyle intervention in those with a BMI >35 kg/m² at study initiation (3).

Thus, the three-arm study of the DPP demonstrated the feasibility of identifying and enrolling a high-risk patient population with IGT and an elevated fasting plasma glucose level into a prevention program. Furthermore, we have demonstrated in a randomized, prospective manner that both pharmacologic therapy with metformin and intensive lifestyle management, with the goal of increasing physical activity and achieving a 7% mean weight loss, significantly and substantially reduced the development of diabetes during a 2.8-year mean follow-up period.

TROGLITAZONE ANALYSIS

The analysis of the troglitazone cohort within the DPP is complicated by the premature termination of the use of that drug and the unblinding and subsequent intervention in those subjects in that treatment arm. Despite these limitations, these subjects continued to undergo follow-up until termination of the DPP, and outcome measures were obtained according to treatment protocol. Subsequent analysis of this cohort was undertaken to determine whether troglitazone reduced the incidence of diabetes during its administration and whether any effect persisted after its discontinuation (6). This analysis incorporated those subjects randomized between 1996 and 1998 before the discontinuation of the troglitazone arm. Approximately 580 subjects were randomized to each of the four treatment arms, for a total of 2,343 in this analysis. The mean duration of exposure to troglitazone, however, was limited to approximately 10 months. As previously stated, the troglitazone intervention was discontinued after a fatal case of liver failure. This was the only fatality in the troglitazone group (three fatalities occurred in the placebo group). Among the troglitazone-treated participants, 4.3% had liver enzyme elevation ≥ 3 times the upper limit of normal at least once during their treatment, and 1.2% had documented liver enzymes ≥ 10 times the upper limit of normal during treatment exposure. The mean body weight of this study group increased from 93 kg to 97 kg during approximately 1 year of exposure to troglitazone, significantly greater than the weight changes observed in the other three treatment groups. Despite weight gain during study observation, the incidence of diabetes was significantly reduced by treatment with troglitazone in comparison with both placebo and metformin (Fig. 1). No significant difference was found in the protective effect of troglitazone in comparison with intensive lifestyle intervention during the 1.5-year follow-up.

On June 4, 1998, troglitazone therapy was discontinued in all study participants, and subsequent evaluation with semiannual fasting plasma glucose levels and annual glucose tolerance testing revealed a diabetes incidence rate among the troglitazone-treated group to be identical to that of the placebo-treated cohort. Thus, despite troglitazone-induced increases in body weight, troglitazone treatment resulted in a 75% reduction in diabetes incidence during its short (10-month mean) period of use, but after discontinuation, it appears to have limited long-term effect on the future development of diabetes.

CARDIOVASCULAR RISK FACTORS

One of the secondary outcome studies prospectively identified in the DPP was the effect of treatment interventions on the development of cardiovascular disease (CVD) and CVD risk factors (1). At baseline, a history of CVD was uncommon, with only 1% of study subjects providing a history of myocardial infarction and another 1% indicating a history of stroke. Approximately 30% of subjects either had a history of or were being treated for hypertension, and 44% were being treated for elevated levels of low-density lipoprotein cholesterol. Cardiovascular events were rare during the 2.8 years of mean follow-up for this cohort. CVD-related mortality occurred in 7 subjects, and 58 nonfatal CVD events were noted. Because of these small numbers, no differences among treatment groups could be discerned.

Over time, those study subjects randomized to placebo had a progressive increase in the prevalence of both hypertension and dyslipidemia (7). This temporal progression was noted in the metformin group as well, with no amelioration of either dyslipidemia or hypertension. In contrast, the intensive lifestyle intervention attenuated the increase in hypertension cumulative prevalence during the 3 years of the study and significantly reduced the prevalence of dyslipidemia. Intensive lifestyle intervention resulted in a 17% reduction in the prevalence of pharmacologic therapy for hypertension compared with either placebo or metformin ($P<0.001$). Additionally, fewer lifestyle intervention study participants required drug therapy for either elevated levels of triglycerides or high levels of low-density lipoprotein cholesterol based on the Adult Treatment Panel II Guidelines, which were in application during the course of the DPP.

The premature discontinuation of the DPP by the Data Safety Monitoring Board precluded the ability of the DPP Research Group to assess either the durability of the interventions on diabetes prevention or the effect on microvascular or macrovascular disease. Both of these issues are currently of major interest in the ongoing Diabetes Prevention Program Outcomes Study (DPP-OS), which will follow the original DPP cohorts for an additional 5 years.

HEALTH ECONOMIC ANALYSIS

The DPP was originally designed to answer the basic question of whether pharmacologic therapy or an intensive lifestyle intervention was capable of delaying or preventing diabetes. The initiation of a clinical trial made one-on-one lifestyle intervention imperative because of the slow identification of subjects and enrollment of those with IGT into the study and the necessary randomization among four treatment arms. Despite the limitations of the clinical trial design, the actual in-trial costs imposed by the established interventions were relatively reasonable (8). Three-year intervention costs specific to the DPP protocol were approximately \$3,200 in the lifestyle group in comparison with \$2,960 in the metformin group and \$497 in the placebo group. Other direct medical care costs, however, were reduced in both the lifestyle and metformin groups as compared with the placebo group (\$4,579 versus \$4,739 versus \$5,011, respectively). Overall, direct and indirect costs were somewhat greater in the lifestyle group than in the metformin or placebo group. When these costs are applied to the number needed to treat to prevent a single case of diabetes, within-trial actual costs of the lifestyle intervention were \$15,655 per case of diabetes prevented (9). This compares with \$31,338 per case of diabetes prevented over 3 years with metformin. When these figures are adjusted for real-world application—generic metformin pricing in comparison with brand name as used in the DPP and group lifestyle intervention in comparison with one-on-one intervention—sensitivity analysis reduces the cost of preventing a single case of diabetes during a 3-year period to \$4,301 with lifestyle intervention and \$11,141 with metformin (9).

If one models the DPP intervention over a lifetime, with the assumption that these interventions will be instituted continuously until subjects die and that the outcome will remain the same as noted during the 2.8 years of the DPP observation, lifetime costs of treatment with intensive lifestyle intervention are only \$1,036 more than placebo (\$51,607 versus \$50,571 for placebo) (10). Metformin therapy with all of its associated medical costs is even more expensive at \$54,594. Despite the increased costs of both lifestyle intervention and metformin, both demonstrate an increase in quality-adjusted life-years (QALY) (0.36 and 0.12, respectively) in comparison with placebo. Thus, from a health utility perspective, lifestyle intervention projected over a lifetime results in less than \$3,000 per QALY gained in comparison with metformin at \$33,000 per QALY. The societal perspective would strongly suggest that lifestyle intervention is an appropriate expenditure of health-care dollars for the outcome achieved. Metformin therapy is still cost-effective, albeit less so, for the change in QALY.

Much has been said about the distinction of delaying the development of diabetes versus actual prevention of diabetes. True prevention can be assessed only at a point in time when the entire cohort has died. Differential development of diabetes before death would then reflect true prevention. By computer modeling, we are able to project the DPP cohort out 30 years beyond the diagnosis of IGT (10) (Fig. 2). If one accepts the incident rates of diabetes observed during the 2.8 years of DPP follow-up and extends them over a lifetime, more than 80% of the placebo-treated group would develop diabetes before dying of any other cause. Metformin therapy has an absolute risk reduction of 7.9%, whereas lifestyle intervention has an absolute risk reduction of 20.2% compared with placebo. To assess the potential in delaying the onset of diabetes, we have examined the duration of time after identification of IGT for 50% of the cohort to develop diabetes. Among the placebo group, 50% have conversion from IGT to diabetes after 6.6 years. Such conversion was delayed by 3.4 years with metformin therapy and by 11.1 years after the diagnosis of IGT with lifestyle intervention. Thus, computer modeling suggests that application of the DPP interventions over a lifetime would result in both delay and prevention of diabetes (10).

CONCLUSION

The DPP and the subsequent DPP-OS remain the largest, most ethnically diverse, diabetes prevention program. During the 2.8 years of observation of the three-arm trial, both metformin and intensive lifestyle intervention effectively delayed or prevented the development of diabetes in a cost-effective manner. Although observation of troglitazone intervention was limited to a mean of 10 months, it also effectively delayed the onset of diabetes. Only lifestyle intervention modified the development of CVD risk factors, but the DPP did not have sufficient statistical power to detect differences in cardiovascular events. The follow-up DPP-OS is designed to evaluate further the effect of DPP interventions on the durability of diabetes prevention as well as the development of both microvascular and macrovascular complications associated with diabetes.

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Fig. 1. Cumulative incidence of diabetes, stratified by treatment group, for the four-arm Diabetes Prevention Program, including the troglitazone treatment group (N = 2,343). Troglitazone (TROG) versus placebo (PLAC), $P < 0.001$; troglitazone versus metformin (MET), $P = 0.02$; troglitazone versus intensive lifestyle (ILS), $P = 0.18$. Adapted from Knowler et al (Diabetes Prevention Program Research Group) (6).

Fig. 2. Computer modeling of Diabetes Prevention Program interventions and outcomes over a lifetime, based on the assumption that interventions are applied until the subjects die and the results are consistent with the observations during the randomized trial. *IGT* = impaired glucose tolerance; *solid line* = placebo; *dashed line* = metformin; *dotted line* = intensive lifestyle intervention. Adapted from Herman et al (Diabetes Prevention Program Research Group) (10).

Table 1
Cumulative Risk of Developing Diabetes and Effect of Interventions in Diabetes Prevention Program

Factor	Placebo	Metformin	Lifestyle
Incidence of diabetes (% per year)	11.0	7.8	4.8
Reduction in incidence compared with placebo (%)	...	31	58
Number needed to treat to prevent 1 case in 3 years	...	13.9	6.9

Adapted from Knowler et al (Diabetes Prevention Program Research Group) (3).