# The Prevention of Type 2 Diabetes: Are We Ready for the Challenge?

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The increase in the prevalence of diabetes during the past 20 years is alarming. Recent data presented by the American Diabetes Association (ADA) reported that 17 million Americans, or 6.2% of the population, now have diabetes. Of these 17 million, 5.9 million, or close to 35%, have undiagnosed diabetes. In the approximately 30 minutes that it would take the average reader to read this entire issue of *Clinical Diabetes*, about 46 patients will be newly diagnosed with diabetes.

Recent research efforts, especially for type 1 diabetes, have been to find a "cure." Although that would be a wonderful discovery, much of our research to date has focused on the treatment of hyperglycemia and the management of diabetes-related complications. From a public health standpoint, it is clear that prevention of diabetes, both type 1 and type 2, would have even more far-reaching implications than either of these other goals.

Diabetes is the leading cause of adult blindness (12,000–24,000 new cases each year), end-stage renal disease (more than 114,000 cases of diabetes-related dialysis or transplantation in 1999), and non-traumatic lower extremity amputation (82,000 diabetes-related amputations between 1997 and 1999). Heart disease is the leading cause of death in people with diabetes,

who have a two- to fourfold higher risk for developing it than that of the general population. The costs of care for diabetes and its complications are staggering and difficult to quantify. Conservatively, total costs for diabetes exceed $98 billion per year. Although interpreting the magnitude of these costs in terms of either human suffering or dollars is difficult, it seems clear that the prevention of diabetes deserves much more attention.

In the past year, several studies have provided hope that type 2 diabetes indeed can be prevented. In a Finnish study, 522 obese subjects with impaired glucose tolerance (IGT, a precursor to type 2 diabetes) were randomized to receive either routine diet and exercise counseling (control group) or intensive individualized instruction about weight loss, food intake, and physical activity (intervention group).[1] After 3.2 years, there was a 58% relative reduction in the progression to diabetes in the intervention group.

Closer to home, the Diabetes Prevention Program (DPP) recently reported its results.[2] The study involved 3,234 subjects with IGT, including 45% from minority groups. Subjects were randomized to metformin (Glucophage) therapy; intensive nutrition and exercise counseling ("lifestyle group"); or a placebo group, whose members received standard diet and exercise instructions.

After an average follow-up of only 2.8 years, a 58% relative reduction in the progression to diabetes was observed in the lifestyle group. Subjects who received metformin had a 31% relative reduction in developing diabetes. Importantly, lifestyle changes were particularly efficacious in the subgroup of subjects who were over the age of 60 years. Overall, metformin was much more effective in the younger subjects.

There is even more reason for optimism. In the Troglitazone in the Prevention of Diabetes (TRIPOD) study, 235 Hispanic women with a history of gestational diabetes (a strong risk factor for subsequent development of type 2 diabetes) were randomized to receive either troglitazone (Rezulin) before it was removed from the U.S. market or placebo. After a median follow-up of 30 months, the women who received troglitazone had a 56% relative reduction in the development of diabetes. Women who had received troglitizone before its removal from the market still had a beneficial effect during the 8 months of the study that took place after the drug was stopped (Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP, unpublished observations). Although it would be premature to conclude that our currently available thiazolidinediones, namely rosiglitazone (Avandia) and pioglitazone (Actos) would have the same benefit as troglitizone, these early data from TRIPOD suggest that we should aggressively test our newer drugs in high-risk populations.

What are the implications of these studies? First and foremost, we can conclude that the natural history of the development of type 2 diabetes can be altered. This is wonderful news. Furthermore, taken together, the Finnish study and the DPP suggest that type 2 diabetes can be delayed or prevented with a safe, inexpensive therapy, with the understanding that exercise-related injuries are not uncommon, especially in people who are new to an exercise program.

The flip side to our optimism is that we currently live in a society that has become more sedentary and obese. Indeed, this is likely the main reason we have seen such an increase in the incidence of type 2 diabetes in the first place. The increased availability of "fast foods" for our children, the lack of physical activity (including a decrease in physical education instruction in our schools), the increase in our dependence on the automobile, and other unhealthy societal developments are taking their toll.

These studies are telling us that, if we can reverse our current lifestyle trends, we can reduce the burden of diabetes. Unfortunately, lifestyle changes are perhaps the most difficult for all of us. So that will be our next challenge as we try to alter the natural history of type 2 diabetes. It would be interesting to see how many New Year's resolutions related to diet, exercise, and weight loss are upheld for an entire year. I suspect that few of us can make such changes over the long term.

Starting on page 109 of this issue, we are reprinting the recent ADA position statement, "The Prevention or Delay of Type 2 Diabetes."[3] This document reviews all of the current literature and recommendations regarding diabetes screening (including screening tests) and possible prevention.

Some readers may be disappointed to learn that, although the DPP showed a modest effect from metformin therapy, current recommendations do not support the use of any pharmacological intervention for the delay or prevention of type 2 diabetes. Costs, side effects, and relative ineffectiveness compared to lifestyle modifications are the main reasons for this. Although I agree with this conclusion, I am hopeful that future studies using newer insulin sensitizers will be at least as effective as the TRIPOD study in preventing type 2 diabetes. In the meantime, it would be premature to initiate any drug solely for the purpose of attempting to prevent type 2 diabetes.

Now, our attention must turn to translating these recommendations for clinical practice. Do primary care physicians have the time and resources to counsel patients on appropriate lifestyle changes? Is reimbursement for the time this will take adequate? Do we teach enough about these successful lifestyle modifications to our medical students and residents?

Subjects in the lifestyle arm of the DPP met with a case manager 16 times over the first 6 months and generally monthly thereafter. At 3-month intervals, these subjects were offered exer-

cise and weight-loss classes lasting 4–6 weeks. The real challenge now, in my view, is to change the lifestyle not only of individuals at high risk of some day developing type 2 diabetes, but also of our entire society. If we could achieve that lofty goal, we wouldn't have to face the difficult challenge of singling out all of those who are destined to develop type 2 diabetes, and we would be able to expect that our general population would be healthier overall.

## REFERENCES

[1]Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001

[2]The DPP Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002

[3]American Diabetes Association and National Institute of Diabetes and Digestive, and Kidney Diseases: The prevention or delay of type 2 diabetes (Position Statement). *Diabetes Care* 25:742–749, 2002