EDITORIAL (SEE DPP RESEARCH GROUP, P. 977)

Prevention of Type 2 Diabetes

What is it really?

The current epidemic of type 2 diabetes in developed countries is occurring at three levels. First, more and more individuals are in positive calorie balance and accumulating fat in their bodies; they are becoming obese. Second, many of those obese individuals partition sufficient lipid in their livers and muscles and/or generate sufficient hormonal signals from fat cells to create insulin resistance. Third, pancreatic β-cells progressively fail in some individuals as they attempt to compensate for insulin resistance by increasing insulin output on a chronic basis. The β-cell failure tends to be slowly progressive over time and leads to progressively rising glucose levels that, when they become dangerous for eyes, kidneys, and nerves, define type 2 diabetes.

Prevention of type 2 diabetes requires arrest of the progressive β-cell dysfunction and stabilization of glucose concentrations at nondiabetic levels. Anything short of this arrest and stabilization will only delay the onset of type 2 diabetes. Theoretically, type 2 diabetes could be prevented or delayed by three types of interventions: *1*) interventions that limit fat accumulation in the body (less obesity = less insulin resistance); *2*) interventions that uncouple obesity from insulin resistance (less insulin resistance = less β-cell failure); and *3*) interventions that directly preserve β-cell mass and/or function, despite the high secretory demands imposed by insulin resistance (better β-cell function = less diabetes).

Current efforts to prevent type 2 diabetes have used interventions that modify obesity and/or insulin resistance or that change glucose levels directly. The studies have generally not focused on the end points of stable glycemia and β-cell function. Rather, they have focused on reducing the fraction of patients with slightly elevated glucose levels (e.g., impaired glucose tolerance or "IGT") who "cross the line" to diabetes, where the risk of microvascular complications begins. The studies have been conducted over periods of time that are short relative to the years that are required for the development of diabetes. Studies of such short duration will reveal a reduction in the incidence of diabetes if active interventions stabilize glucose at nondiabetic levels in some or all individuals (real diabetes prevention). Interventions that lower glucose levels acutely without changing the rate of increase and interventions that slow rather than arrest increasing glucose levels will also cause an apparent reduction in the incidence of diabetes. However, these latter two types of interventions delay rather than prevent diabetes. Eventually, the treated individuals will develop diabetes because their glucose levels continue to rise.

Recent claims of diabetes prevention must be tempered by the reality that, in most of the studies conducted to date, only a slowing of the rate of development of diabetes has occurred. Diabetes-free survival curves or cumulative incidence curves in the U.S. Diabetes Prevention Program (DPP) (1) and the STOP-NIDDM trial (2), reveal a 25–58% reduction in diabetes risks in groups that received active interventions with diet and exercise, metformin, or acarbose during medians of 2–3 years of follow-up. However, the treated groups continued to develop diabetes at rates that were much greater than zero throughout the trials. In other words, glucose levels continued to rise during the active interventions, indicating delays of 1–2 years in the onset of diabetes rather than true prevention of the disease. Delaying diabetes for a year or two might benefit patients by delaying their time to development of chronic diabetic complications, but delay cannot be equated with diabetes prevention. Prevention requires an arrest of rising glucose concentrations and, ideally, demonstration of stable B-cell function.

In the Troglitazone in Prevention of Diabetes (TRIPOD) study (3), the cumulative incidence of diabetes dropped to zero in subjects treated with troglitazone for >3 years, suggesting true diabetes prevention in a subset of the cohort. The cumulative incidence of diabetes was also zero after 5 years of diet and exercise treatment in the Finnish Diabetes Prevention Study (4), suggesting prevention in a subset of the treated subjects. In the TRIPOD study, subjects who remained free of diabetes during drug treatment had stable glucose concentrations and stable B-cell function over a 4.5-year period of time, consistent with true diabetes prevention. Unfortunately, troglitazone treatment failed to treat insulin resistance in approximately one-third of the subjects in TRIPOD. Those individuals were not protected from diabetes.

The issue of preventing versus delaying type 2 diabetes is closely related to the issue of whether putative diabetes preventatives really modify the natural history of metabolic derangements that lead to diabetes. This latter issue is particularly relevant when the intervention is a pharmacological agent known to lower glucose concentrations. Take as an example a drug that acutely lowers glucose concentrations by 20 mg/dl in patients with IGT. Even if that drug has no impact on the rate at which glucose levels rise, treatment will give the appearance of diabetes prevention during a fixed duration of follow-up. The reason is simple—individuals on the drug will have lower glucose concentrations than those in a nontreated control group. Even though glucose levels are rising at the same rate in each group, the treated patients will "cross the line" to diabetes somewhat later. The apparent prevention of diabetes will really be a masking of the underlying disease process. Stopping the drug will result in a rapid increase in glucose levels and a reduction in the apparent protective effect of the intervention. The lowering of glucose levels could have an important effect to delay long-term diabetic complications (much like treating established diabetes), but the resultant masking of underlying progression to diabetes should not be confused with arrest of the primary process(es) that actually cause diabetes.

In this issue of *Diabetes Care*, the DPP Research Group reports the results of

post-trial testing of glucose tolerance among individuals with IGT who participated in the metformin and placebo arms of the DPP (5). As reported earlier (1), testing for diabetes at 6-month intervals while subjects were given study medications revealed a 31% reduction in the risk of diabetes in patients assigned to metformin. At the end of the DPP, study medications were stopped for 1–2 weeks and testing for diabetes was repeated. During this short post-trial washout period, the frequency of new cases of diabetes in people who had been assigned to metformin during the trial was 49% higher than in people who had been assigned to placebo. The number of new cases was small in both groups due to the short period of observation, so the statistical probability of a real difference in diabetes rates was 0.098 during the washout period. When the cumulative incidence rates of diabetes between the start of the trial and the end of the post-trial washout were compared between groups, the metformin group had a 25% reduction in the overall incidence of diabetes. This reduction is somewhat less than the 31% reduction observed while patients were still taking study medications.

What do these new observations from the DPP mean? They mean that once study medications were stopped, glucose levels increased more or faster in the metformin than in the placebo group. In other words, some of the apparent protection from diabetes in the metformin group was due to an acute effect of the drug to lower glucose levels, especially fasting glucose levels (5), without modifying the underlying disease process. Approximately 1–2 weeks after metformin was stopped, the fraction of people who had diabetes was still lower than that in the placebo group. However, it is not clear whether glucose levels had stopped increasing at that time. Moreover, the authors do not tell us whether or in what fraction of participants glucose levels had increased from values at study entry. Thus, while it is true that some protection from crossing the line to diabetes persisted 1–2 weeks after metformin was stopped, it is not clear whether the drug arrested the increasing glucose concentrations that eventually lead to diabetes. The cumulative incidence curves from the DPP strongly suggest that it did not. Stopping acarbose in the STOP-NIDDM study also resulted in an increase in glucose levels and in cases of diabetes, suggesting that some of the protective effects of that drug were due to acute glucose lowering. In contrast, when participants in the TRIPOD study were tested 8 months after they had stopped placebo or troglitazone, the group that had been diabetes-free on troglitazone enjoyed continued protection from diabetes, along with stability of glucose levels and B-cell function, while people who had been on placebo continued to develop diabetes. This pattern is indicative of real diabetes prevention in the troglitazone group. As stated previously, prevention of diabetes was limited to women in whom troglitazone improved insulin sensitivity.

Where do these observations leave the evolving field of prevention of type 2 diabetes? For researchers who are designing or conducting prevention trials, I hope they point to a need to rethink study end points. Diabetes is a serious disease, and reducing the rate at which people develop the disease is important. However, investigators who want to study diabetes prevention must keep in mind that the disease usually results from progressive loss of B-cell function leading to progressive hyperglycemia. Simply demonstrating that fewer people cross the line to diabetes in a relatively short interval of time does not prove that diabetes has been prevented. Outcomes ideally should include measures of B-cell function in relation to insulin resistance, looking for stability over time. In the absence of such measures, stability of glycemia should be assessed to determine whether diabetes is prevented or only delayed in groups that receive active treatment. Of course, testing after a meaningful postdrug washout period should be included if the intervention is a drug known to lower glucose levels. Finally, prolonged follow-up to look for an impact on chronic diabetes complications would be ideal.

For clinicians who are managing patients at high-risk for diabetes, there are several options available to at least slow the rate at which diabetes develops. Behavioral programs to achieve modest weight reduction and increased physical activity can slow the development of diabetes (1,4). More intensive programs are likely to have more dramatic effects to truly prevent diabetes, but data demonstrating such effects are currently lacking. Nevertheless, diet and exercise programs should be the first step in managing high-risk patients (e.g., patients with IGT or impaired fasting glucose). Monitoring for success should focus not only on achievement of diet and exercise goals, but also on stability of glycemia. Patients whose glucose levels do not rise during a given behavioral intervention have achieved the goal of diabetes prevention, stability. People whose glucose levels rise despite a behavioral intervention are not responding adequately to the intervention. Consideration should be given to pharmacological therapy in those individuals. Based on the available data, metformin and acarbose can delay the development of diabetes but probably do not prevent the disease. Troglitazone prevented diabetes in a subset of the TRIPOD cohort via a mechanism that is likely to apply to other thiazolidinedione drugs as well. Troglitazone also stabilized glucose levels and β-cell function when given as soon as diabetes was diagnosed by annual oral glucose tolerance tests. Thus, the optimal timing of pharmacological interventions remains to be determined. However, based on the progressive nature of β-cell failure in type 2 diabetes, once the disease becomes clinically apparent (6), early rather than late intervention with drugs that ameliorate insulin resistance seems prudent.

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References

1. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
2. Chaisson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose for prevention of type 2 diabetes: the STOP-NIDDM randomised trial. *Lancet* 359: 2072–2077, 2002
3. Buchanan TA, Xiang AH, Peters RK, Kjos

SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic B-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51: 2769–2803, 2002
4. 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, Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
5. Diabetes Prevention Program Research Group: Effects of withdrawal from metformin on the development of diabetes in the Diabetes Prevention Program. *Diabetes Care* 26:977–980, 2003
6. UKPDS Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 352:837–853, 1998