Applying the Lessons of the DPP to Clinical Practice

Reviewed by Silvio E. Inzucchi, MD, and Robert S. Sherwin, MD

STUDY

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

SUMMARY

Objective. To determine whether improvement in risk factors for type 2 diabetes (mild hyperglycemia, overweight, sedentary lifestyle) with lifestyle change or metformin (Glucophage) can prevent or delay diabetes.

Design. A multicenter (27 sites), randomized, clinical trial.

Subjects and methods. A total of 3,324 adults with impaired glucose tolerance (IGT) and elevated fasting plasma glucose (FPG) (95–125 mg/dl) were randomized to receive placebo, metformin (850 mg twice daily), or intensive lifestyle change (weight loss ≥7% body weight and moderate physical activity ≥150 minutes per week), and followed for 3 years.

Results. At baseline, the mean age was 50.6 years, body mass index (BMI) was 34.0 kg/m^2, FPG was 106.5 mg/dl, and 2-hour plasma glucose was 164.6 mg/dl. Non-white ethnic patients comprised 45% of the study population. The incidence of diabetes during an average follow-up of 2.8 years was 11.0, 7.8, and 4.8 cases per 100 person-years in the three assignment groups, respectively. The incidence of diabetes was reduced by 58% in the lifestyle group and by 31% in the metformin group.

Conclusion. Lifestyle intervention and metformin therapy both reduced the incidence of diabetes in patients at high risk, with the former being more effective than the latter.

COMMENTARY

The Diabetes Prevention Program (DPP) assessed the long-held notion that diet and exercise could prevent or delay type 2 diabetes. Using different study designs in smaller cohorts, the effectiveness of lifestyle intervention has been demonstrated previously by both Chinese[1] and Finnish[2] investigators. The DPP was the first to also assess the effectiveness of early treatment with an antihyperglycemic agent.

The DPP's results are impressive. Patients who undertook either of the two active treatments were less likely to experience deterioration in glycemia. The cumulative incidence of diabetes at 3 years was 28.9, 21.7, and 14.4% in the placebo, metformin, and lifestyle groups, respectively. Based on these rates, the number of people needed to treat for 3 years to prevent one case of diabetes calculates to 6.9 for lifestyle change and 13.9 for metformin. Treatment was equally effective in both sexes and in all races and ethnic groups.

Lifestyle change was most effective in those with lower 2-hour glucose levels at baseline. Metformin was less effective in those with lower BMI or with a lower fasting glucose level. The advantage of lifestyle intervention over metformin was most prominent in older and in less obese individuals.

Given the severe complications of diabetes, preventive strategies for the hundreds of millions of patients worldwide with pre-diabetes seems logical. Therefore, the DPP's implications for clinical practice are profound. However, whether the most effective strategy—lifestyle change—can be applied successfully in our offices and clinics remains uncertain.

At first glance, the modest weight loss (~10 lb) and increase in activity seems eminently achievable. But on further inspection, translating these data to everyday practice will be difficult. First, subjects who expressed interest in participating in the DPP were already motivated and saw their involvement in the project as a means to achieve better health. Second, a four-step recruitment and screening process was developed to identify eligible patients. It is conceivable that those who were less motivated and who might have been less likely to follow the study protocol were lost in this process. Third, the resources necessary to ensure proper implementation of the diet and exercise program were substantial. Lifestyle intervention subjects were given a 16-lesson curriculum that covered nutrition, exercise, and behavior modification. This was taught by specialized case managers on a one-to-one basis, followed by group sessions to reinforce behavior change. When necessary, individual sessions continued. Some sites provided incentives to achieve the lifestyle goals. In today's health care environment, it would be premature to assume that practitioners could easily implement the DPP lifestyle protocol, much less duplicate its outstanding results.

Although it is imperative that health care providers counsel patients about healthy eating, weight loss, and exercise,[3] many barriers hamper this

behavior. These include time constraints, reimbursement disincentives, lack of resources, and perceptions that such advice may be ineffectual. The recent Activity Counseling Trial involving 874 sedentary patients in the primary care setting suggested that exercise counseling was ineffective at increasing self-reported physical activity.[4] Similar results have been reported elsewhere.[5]

Such concerns should not dissuade us from trying to apply what we can from the DPP. Identifying patients at risk for type 2 diabetes is as important as ever. These individuals will benefit, at the very least, from regimens aimed at cardiovascular disease prevention. For those patients who are highly motivated and capable of enacting lifestyle change, discussion regarding diet and exercise is indicated.

Given the time and financial limitations of most primary care practices, the design and follow-up of any formal or regimented program will necessitate collaboration with other health care professionals, including dietitians, diabetes educators, exercise physiologists, and behavioral therapists. Access to these professionals will likely be limited through most insurers. The health care community must speak with one voice to encourage policy makers to mandate that such programs be viewed as necessary, and therefore covered, services for at-risk patients. In some settings, highly motivated and informed patients may be willing to either pay the associated costs themselves or seek out lower-cost alternatives, such as community or work-based exercise programs. Evidence-based research on wellness counseling, motivational techniques, and enacting lifestyle change is needed.

A second important lesson of the DPP is that in those patients who are unwilling or unable to undertake lifestyle change, early off-label therapy with an antihyperglycemic agent such as metformin will likely slow their progression to diabetes, although to a significantly lesser degree than would lifestyle change. The number needed to treat in this manner is within a range deemed reasonable for other widely used health care interventions. We await the all-important cost-effectiveness analyses that will follow the initial DPP report. Preliminary reports appear encouraging.[6] Such analyses are mainly determined by the impact of interventions on future complications rather than disease appearance and are therefore not intuitively obvious.

The DPP raises many questions. Is diabetes truly being prevented or simply delayed? If the latter, are the interventions still worthwhile? Because the study design was based on the initial diagnosis of IGT, should the oral glucose tolerance test reemerge as an important case-finding tool? At what point, if any, do we proceed from encouraging lifestyle change to pharmacotherapy? Will glucose-lowering drug therapy reduce the risk of cardiovascular disease in IGT? Would the combination of lifestyle change plus metformin yield additional risk reduction? Finally, how do we place the DPP results in the context of more recent reports suggesting similar benefits in diabetes prevention from other drug classes, such as the insulin-sensitizing thiazolidinediones,[7] α-glucosidase inhibitors,[8] angiotensin-converting enzyme inhibitors,[9] angiotensin II receptor blockers,[10] and HMG CoA reductase inhibitors?[11] Answers will likely be forthcoming, as further research becomes available, as practice guidelines emerge, and as clinical experience grows.

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Silvio E. Inzucchi, MD, is an associate professor of medicine and clinical director of Endocrinology, and Robert S. Sherwin, MD, is the C.N.H. Long Professor of Medicine and director of the Yale Diabetes Endocrinology Research Center at Yale University School of Medicine in New Haven, CT.

Note of disclosure: *Dr. Sherwin serves on advisory board panels for Bristol-Myers Squibb, Takeda, and Bayer Pharmaceuticals, which make drugs for the treatment of diabetes.*