Published in final edited form as:

Arch Intern Med. 2011 August 08; 171(15): 1361–1362. doi:10.1001/archinternmed.2011.367.

Prevention of type 2 diabetes: comment on “Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels”

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Preventing type 2 diabetes mellitus (T2DM) has been studied in several randomized clinical trials in adults at high risk of developing diabetes.^{1–6} Most enrolled only persons with impaired glucose tolerance (IGT) during an oral glucose tolerance test (OGTT). Other high-risk characteristics often employed included obesity and elevated fasting plasma glucose (FPG). All these studies had OGTT-diagnosed diabetes as the primary outcome, although exact definitions differed among studies.

Some of these trials tested lifestyle weight-loss interventions; some used drugs; and some used both. All reported benefit, to varying degrees, of most interventions, although the extent to which studies without beneficial effects were not published is unknown. Two key questions remain: 1) What is the preferred intervention or combination of interventions? 2) How should persons be selected for intervention?

The greatest risk reductions (approximately 75%) were achieved with the thiazolidinedione drugs troglitazone⁴ or pioglitazone.⁶ Troglitazone is no longer available because of its liver toxicity. All thiazolidinediones have worrisome side effects including edema and sustained weight gain. By contrast, metformin, although less effective in reducing diabetes incidence, causes modest weight loss that is sustained for at least 10 years.⁷ In two trials, lifestyle weight-loss interventions resulted in large (58%) diabetes risk reductions.^{2,3} Comparing the effects of different drugs with each other or with weight loss is difficult, however, because most trials tested only one intervention, and the trials differed in eligibility criteria, outcome assessment, drug dosage, lifestyle intervention intensity, and treatment of the comparison group. The DPP compared lifestyle and metformin directly and found that lifestyle was more effective, but in the Indian Diabetes Prevention Programme, metformin, weight loss intervention, and both in combination had similar effects.⁵

Data on long-term safety and benefit of lifestyle or drug interventions for preventing T2DM are few. Little evidence supports the attractive hypothesis that preventing the rise in glycemia to diabetes diagnostic levels will also prevent diabetes complications, but long-term follow-up of the DPP should be informative.⁷ Lacking such evidence, lifestyle interventions might be preferred over drugs because the former reduce diabetes incidence, have other health benefits, and need not be limited to persons at high risk of T2DM.

It is less clear who should be offered diabetes prevention interventions, because evidence for prevention comes from trials conducted only in adults at high risk of diabetes to enhance power to detect meaningful treatment effects. Most T2DM prevention trials have enrolled

only persons with IGT. Other predictors of T2DM, such as body mass index, FPG or HbA1c, might also be used instead of IGT to identify persons for clinical trials or prevention services.⁸ Despite abundant evidence that these and other factors predict T2DM, we lack evidence that intervention will reduce diabetes incidence in persons selected by such criteria or among populations without identified risk factors. Such evidence is critical for widespread implementation, however, because the OGTT required for identification of IGT is cumbersome, poorly reproducible, and not routinely performed in most settings. The randomized clinical trial of Saito et al. (this issue) is, therefore, highly relevant. Eligibility was based on elevated FPG (100 to 125 mg/dl or 5.5 to 6.9 mmol/L, defined as impaired fasting glucose or IFG), similar to the FPG eligibility criteria of the DPP, but IGT was not required. OGTTs were used to exclude diabetes at entry and to define the diabetes outcome. The intensive lifestyle intervention reduced diabetes incidence by 44% compared with standard care (i.e., hazard ratio = 0.56), results similar to the other lifestyle intervention trials. The risk reduction was greater among subgroups at higher baseline risk as determined either by IGT, FPG ≥ 110 mg/dl, or HbA1c $\geq 5.6\%$ by the Japan Diabetes Society method (see their Table 2). These high-risk subgroups contained fewer than half the participants but the majority of the outcome events (baseline HbA1c was $\geq 5.6\%$ in 29% of the participants who experienced 57% of the outcomes). In those with HbA1c $\geq 5.6\%$, risk was reduced by 76%, the greatest risk reduction of any subgroup presented. There was no risk reduction among the subjects with isolated IFG (i.e., IFG with normal 2-hour glucose), although the effect estimate was very imprecise in this lower-risk group that experienced only 22 outcome events (from Table 2). This trial, therefore, showed that other glycemic measures, such as elevated HbA1c or IGT, refine the high-risk characteristics of people initially identified through FPG. These results support suggestions that HbA1c could be used to identify persons for prevention interventions⁸ and confirm that intervention effects are hard to establish or nonexistent in persons without multiple risk factors. We still lack data on T2DM prevention in persons with elevated HbA1c but without elevated fasting or post-load glucose concentrations.

High fasting or post-load plasma glucose, obesity, and physical inactivity predict T2DM, suggesting that interventions targeting these risk factors in the general population will reduce the incidence of T2DM. Clinical trials, including the present one, have not tested prevention effects in average-risk individuals, however, presumably because of inadequate power. Measures such as FPG, HbA1c and body mass index that can be readily obtained in population screening, as well as the more cumbersome OGTT, may help identify those most likely to benefit from diabetes prevention efforts. Although a number of genetic variants affect T2DM susceptibility, they add little to readily obtained clinical measures in short-term disease prediction, and persons at greatest genetic risk benefit at least as much from preventive interventions as those at lower genetic risk.^{9,10} Current knowledge does not indicate a need to test genetic susceptibility in selecting individuals for prevention or the optimal interventions, although this is likely to change with results of further research. In summary, we have good methods for preventing T2DM in high-risk persons, but in addition to improving these interventions, we should determine which individuals can benefit the most from them.

Acknowledgement.

Work on this commentary was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases.

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