Family Physician Corner

Landmark Studies of Prevention or delay of type II diabetes – Part II

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In the previous paper, the brief backgrounds of five well-designed randomized controlled trials on preventing or delaying type II diabetes were outlined. In this paper, based on the recent American Diabetes Association (ADA) position statement, "The Prevention or Delay of Type 2 Diabetes"), the practical implications of these trials will be discussed. These trials raise the following issues: why diabetes prevention should be attempted? Who are the potential candidates for screening and intervention? How should diabetes prevention strategies be performed and how do they differ from diabetes treatment? Finally, the main areas of further research are highlighted.

The first and the leading implication is that the natural history of the development of type 2 diabetes can be altered and thus delayed or prevented by initiating a prevention program.

The program has at least five conditions that should be met to justify its initiation to prevent a disease. First, the disease should be an important health problem that adds a significant burden on the affected population. Obviously, given that 30% of Bahraini population is affected, diabetes satisfies this criterion. Second, the early development and natural history of the disease should be well-understood to identify parameters that measure its progression to a disease state. Hyperglycemic states, impaired fasting glucose (IFG) and the 2-hours impaired glucose tolerance test (IGT) are strongly related to the incidence of diabetes. They are the best tests to predict future diabetes, especially in the presence of risk factors such as age, family history, blood pressure, etc. Third, the tests that are used to detect the pre-disease state should be safe, acceptable, and predictive. This is applicable on both measurement of fasting plasma glucose (FBS) and the 2-hours oral glucose tolerance test (OGTT). Fourth, there should be safe, effective, and reliable method(s) to prevent or at least delay the disease from occurring. Taken together, the Finnish study and the Diabetes Prevention Program trial (DPP), type 2 diabetes can be delayed or prevented with a safe, inexpensive therapy. In the Finnish study, the number needed to treat (NNT) for 1 year to prevent one case of diabetes was 22, and the NNT was 5 to prevent one case in 5 years. In the DPP, the NNT to prevent one case of diabetes in 3 years through lifestyle modification was 7, and the NNT for the same period is

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using metformin, as the intervention was 14\textsuperscript{4}. None of the interventions were associated with any major harmful effects. These data suggest that these interventions are very safe and efficacious. Furthermore, these interventions have beneficial effect on reducing cardiovascular risks in addition to diabetes prevention. Fifth, the effort of screening individuals who are at high risk of getting the disease and the expense of the intervention(s) should be cost-effective. No studies have been published yet on the cost-effectiveness of screening to detect pre-diabetes (IFG or IGT) or to prevent or delay the onset of diabetes. Furthermore, and beyond the financial aspects, high risk individuals can react negatively to whatever label they are given, which can promote anxiety and be socially disruptive.

Based on the above, it is clearly shown that individuals at high risk can be identified and that diabetes can be delayed or even prevented through establishing a lifestyle-modifying program that includes exercise and perhaps pharmacological interventions. The question arises: are we ready for this challenge bearing in mind that we live in an affluent society characterized by the extensive use of housemaids, lack of exercise, dependence on automobiles and widespread availability of fast food leading to the increasing incidence of obesity? The explanation for the high prevalence of diabetes especially among females is readily apparent.

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 the most difficult for all of us: so altering the natural history of type 2 diabetes through lifestyle interventions should be a challenge that involve coordinated team work from the public, health care professionals, government, and society. Otherwise, one would expect that few of us could make such changes over the long term.

The second issue discusses the potential candidates for screening and intervention. Except the DPP which required FPG value less than the current cutoff point for diabetes (i.e., $<126 \text{ mg/dl}$ but $>95 \text{ mg/dl}$), most of the diabetes prevention trials required that subjects have IGT (defined as FPG level $<140 \text{ mg/dl}$ and a 2-h OGTT value between 140 and 199 mg/dl) as the main enrollment criterion. Using the current definitions of IFG, IGT, and diabetes, the 2-h OGTT appears to identify more people who have impaired glucose homeostasis and, thus, more people who will progress to diabetes. Regarding the tests themselves, the FPG test is more convenient to patients, more reproducible, less costly, and easier to administer than the 2-h OGTT. For all the above reasons, either the FPG test or 2-h OGTT can be used to screen for pre-diabetes (IFG or IGT).

No study has explicitly addressed the age at which screening should begin, the optimal frequency of screening, or other indications for screening. However, data suggest that pre-diabetes (IFG or IGT) is much more likely to be detected in overweight middle-aged individuals than in younger lean individuals. Hence it was suggested that opportunistic screening to detect pre-diabetes (IFG or IGT) should be considered in individuals $\geq 45$ years of age, particularly in those with a BMI $\geq 25 \text{ kg/m}^2$. Given the age-related incidence of diabetes and the rate of progression to diabetes in normoglycemic middle-aged subjects, repeat testing at 3-year intervals seems reasonable.
The case for screening is strengthened by the fact that screening will not only detect cases of IFG or IGT, but also will detect cases of undiagnosed diabetes. Thus, policies to identify individuals for whom it is appropriate to initiate a diabetes prevention strategy will also identify individuals who should receive treatment for diabetes. Furthermore, because individuals with IFG, IGT, or undiagnosed diabetes are at high risk for cardiovascular disease (CVD), their identification should herald increased surveillance and treatment for hypertension, dyslipidemia, and tobacco use.

The third issue deals with how diabetes prevention should be performed. Is it by Lifestyle changes or medication or both?

The strategies that were used in the trials for preventing diabetes relied on lifestyle modification or glucose lowering drugs that have been approved for treating diabetes. The DPP is the only study, which compared both. In this trial, lifestyle modification was nearly twice as effective in preventing diabetes as metformin (58 vs.31% relative reductions, respectively).

The greater benefit of weight loss and physical activity strongly suggests that lifestyle modification should be the first choice to prevent or delay diabetes. In the two well-controlled studies, the Finnish and DPP trials, considerable efforts were necessary to achieve only modest changes in weight and exercise, but those changes were sufficient to achieve an important reduction in the incidence of diabetes. Modest weight loss (5-10% of body weight) and modest physical activity (30 min daily) are the recommended goals. Due to their benefits on CVD risk reduction, health care providers should urge all overweight or sedentary individuals to adopt these changes, and such recommendations should be made at every opportunity.

Drug therapy to prevent or delay diabetes appears to be much less useful for a variety of reasons. First, in the DPP trial, metformin was found to be considerably less efficacious than lifestyle modification. Second, all glucose-lowering drugs require monitoring, are associated with significant adverse effects, and are contraindicated in some individuals. Third, none of the glucose-lowering agents tested have been evaluated with regard to protection against CVD to nondiabetic individuals. Finally, prescribing a medication to delay the onset of diabetes will increase a patient's total years of drug exposure if diabetes developed and may increase the likelihood of drug adverse effects. Therefore, when all these factors are considered, there is insufficient evidence to support the routine use of drug therapy alone or combined with lifestyle modification to prevent diabetes.

The lifestyle intervention used in the DPP appeared to prevent or delay the onset of diabetes for about 3 years in addition to its CVD risk reduction benefit. Furthermore, lifestyle intervention appears to be very safe, and thus regular monitoring for adverse effects is unnecessary. There is no available data on the cost effectiveness of lifestyle intervention regimens, but low-cost ways to reinforce lifestyle goals and low-cost community-based programs to increase physical activity and avoid unhealthy lifestyle choices are greatly encouraged.
The fourth issue explains how strategies to prevent diabetes differ from those to treat diabetes. It might appear that performing FPG test or OGTT to determine whether a patient has pre-diabetes (IFG or IGT) and then prescribing weight loss and/or exercise in "positive" individuals is no different from using the same tests to screen for diabetes and initiating the same treatment in those with diabetes. However, there are important differences between preventing diabetes and treating diabetes.

First, diabetics should receive additional tests and procedures (eg., foot examination, dilated eye examination, HbA1c measurement, urine protein) to detect complications of hyperglycemia that are not relevant to people with pre-diabetes (IFG or IGT). Second, diabetics are at greater risk for some acute complications (eg., hypoglycemia, increased infections) as well as microvascular complications that have not been documented in individuals with pre-diabetes (IFG or IGT). Third, targets of blood pressure and lipid profile for diabetics are much lower than that for people who have pre-diabetes (IFG or IGT). Finally, diabetics are more prone to social and economic discrimination. Recommending and monitoring a therapeutic regimen without having a disease label placed on an individual may be advantageous as it can reduce the discrimination experienced by diabetics.

At the end, the author in the ADA position statement suggested that many health services research questions should be answered before capitalizing on a preventive diabetes program. These are related to the cost effectiveness of a lifestyle or drug intervention and screening methods of pre-diabetes stage, and whether there are intervention programs that require fewer resources compared to the DPP or Finnish studies, but still achieve comparable or even greater weight reduction and increased physical activity. In addition, further research should investigate what prevention programs can sustain these results on weight reduction and physical activity. It should also investigate the most effective way to combine public awareness, professional education, and health systems policy to ensure identification of those with pre-diabetes (IFG or IGT) and the achievement of a sustained lifestyle modification.

REFERENCES