Counterpoint: Evidence-Based Prevention of Type 2 Diabetes: The Power of Lifestyle Management

The need to prevent type 2 diabetes was recognized as early as the 1920s (1), but surprisingly little was done to apply preventive measures against this disease in subsequent decades (2,3). One of the main problems was the lack of evidence based on well-conducted studies. There were several clinical trials, but they were usually grossly underpowered, had flaws in design and conduct, and most used antidiabetes drugs as the intervention (3). Luckily, firm positive results from several randomized controlled trials (4–10) using lifestyle intervention have become available during recent years. Also, several properly designed and conducted trials using antidiabetes drugs in individuals at high risk, i.e., with intermediate hyperglycemia, have reported favorable results (8,10–14). The bottom line is that these recent trials have unequivocally demonstrated that it is possible to reduce the rate of progression to type 2 diabetes in high-risk individuals with intermediate hyperglycemia.

The Swedish Malmö feasibility study (5) used increased physical exercise and weight control as major intervention strategies to prevent or delay type 2 diabetes in men with impaired glucose tolerance (IGT). Men who received intervention had less than half the risk of developing diabetes in 6 years compared with those who decided not to participate in the diet-exercise program.

In the Chinese Da Qing Study (6), people with IGT were randomized by clinic into one of the four groups: exercise only, diet only, diet plus exercise, and a control group. The cumulative incidence of type 2 diabetes during 6 years was significantly lower in the three intervention groups compared with the control group (41% in the exercise group, 44% in the diet group, 46% in the diet plus exercise group, and 68% in the control group) and remained significant even after adjusting for differences in baseline BMI and fasting glucose.

The Finnish Diabetes Prevention Study (DPS) (7) found that a reduction in body weight achieved through an intensive diet and exercise program was associated with a 58% reduction in the risk of developing type 2 diabetes ($P < 0.001$). Middle-aged men ($n = 172$) and women ($n = 350$) who were overweight and had IGT were individually randomized to an intervention group or to a control group and received conventional advice. The goals of the lifestyle interventions were to achieve a ≥5% reduction in body weight, reduce all fat intake to <30% of energy consumption, particularly reducing saturated fat intake to <10% of energy consumption, increase fiber intake to at least 15 g/1,000 kcal, and undertake a program of moderate physical activity for ≥30 min/day. After 1 year, individuals in the intervention group had achieved a significantly greater mean reduction in body weight compared with the control group ($P < 0.001$). They also demonstrated favorable changes in fasting and postchallenge plasma glucose levels. The reduction in the risk of progression to diabetes was directly related to the magnitude of the changes in lifestyle; none of the participants who had achieved at least four of the five intervention goals in the 1st year developed type 2 diabetes during the trial.

The U.S. Diabetes Prevention Program (DPP) (8) also found that lifestyle modification reduced the incidence of type 2 diabetes by 58% in overweight American adults with IGT. A total of 3,234 adults were randomized to standard lifestyle recommendations plus placebo or 850 mg metformin twice daily or to an intensive lifestyle modification program. The goal of the program was to achieve and maintain ≥7% reduction in body weight through a low-calorie, low-fat diet plus physical activity of moderate intensity for at least 150 min/week. Participants in the lifestyle intervention group had a significantly greater mean reduction in body weight (−5.6 kg, $P < 0.001$) compared with those in the placebo (−0.1 kg) and metformin groups (−2.1 kg). The cumulative incidence of diabetes during the follow-up period was lower in the lifestyle intervention and metformin groups than in the placebo group, with incidence rates of 4.8, 7.8, and 11.0 cases per 100 person-years, respectively. This reduction in incidence can be translated to one case of diabetes prevented for every 7 individuals with IGT treated for 3 years in the lifestyle intervention group, compared with 14 in the metformin group. Lifestyle intervention produced almost identical results in all ethnic groups included in the DPP.

A Japanese lifestyle intervention study (9) among 458 men with IGT resulted in a 67% relative risk (RR) reduction compared with control men during a 4-year trial. Recently, in the Indian Diabetes Prevention Program (10), 531 individuals with IGT were randomized into four groups assigned to: *1*) metformin, *2*) lifestyle modification, *3*) both lifestyle modification and metformin, or *4*) a control group. The cumulative incidence of type 2 diabetes during the median follow-up period of 30 months was significantly lower in the lifestyle modification group (39%), the metformin group (41%), and the lifestyle modification plus metformin group (40%) compared with the control group (55%). Thus, also in this trial, the absolute risk difference was ~15%.

To summarize, these trials have repeatedly confirmed that lifestyle intervention works in all ethnic groups and various social and cultural settings worldwide. Nevertheless, several individuals in the intervention arm of these trials became diabetic. Thus, it seems that lifestyle intervention did not completely remove the risk of diabetes. The DPS, however, has demonstrated that those individuals who changed their lifestyle to the desirable level were protected against diabetes and that those assigned to the intervention group who became diabetic were not able manage to change their lifestyle sufficiently.

LESSONS FROM THE EXTENDED FOLLOW-UP OF THE FINNISH DPS

— After a median of 4 years of the intensive intervention period, the active intervention in the DPS has ceased because it had been un-

equivocally demonstrated that lifestyle intervention prevents type 2 diabetes (7). The DPS participants who had remained free of diabetes when the study closed were further followed for a median of another 3 years, making the overall follow-up time 7 years on average. The extended follow up of the DPS assessed the extent to which the originally achieved lifestyle changes and the reduced risk of diabetes persisted after active lifestyle counseling had been discontinued (15). Diabetes incidence, body weight, physical activity, and dietary intakes of fat saturated fat and fiber were measured. During the overall follow-up period, the incidence of type 2 diabetes was 4.3 and 7.4 per 100 person-years in the intervention and control groups, respectively (log-rank test $P = 0.0001$), indicating a 43% (RR) reduction. The 58% RR during the original active trial period was higher, but this was due to the statistical facts. The cumulative incidences became higher in both groups, which reduced the ratio (RR), whereas the absolute risk difference between the original randomization groups remained about the same or even increased a little. The risk reduction was related to the success in achieving the intervention goals of weight loss, reduced intake of total and saturated fat, increased intake of dietary fiber, and increased physical activity during the original randomized trial period. Importantly, beneficial lifestyle changes initially achieved by the intervention group participants were maintained even after the discontinuation of the intervention; the incidence rates during the post-intervention follow-up period were 4.6 in the original intervention group and 7.2 per 100 person-years in the control group ($P = 0.0401$), indicating a further 36% RR reduction.

Thus, the DPS follow-up for the first time has demonstrated that lifestyle intervention in individuals at high risk for type 2 diabetes not only reduces diabetes risk in the short term when the actual intervention is carried out, but also that effects on lifestyle changes and reduced diabetes risk are long term. For public health services planning, the message is clear that an intensive lifestyle intervention lasting for a limited time can yield marked long-term reduction in the risk of type 2 diabetes in individuals with IGT without a further investment.

ANTIDIABETES DRUGS LOWER BLOOD GLUCOSE, AS LONG AS THEY ARE TAKEN

— Since the early invention of insulin and oral antidiabetes agents, it has been clear that it is possible to lower elevated blood glucose by pharmacotherapy. All clinical trials have shown that blood glucose levels may be reduced to some extent if an antidiabetes drug is taken. Several long-term studies have, however, found that despite active antidiabetes drug therapy, glycemic levels gradually increase in diabetic patients and even exceed the pretreatment values in <10 years (16).

As expected, trials of antidiabetes pharmacotherapy among individuals with elevated plasma glucose have confirmed that plasma glucose levels can be reduced, and similarly, several studies among individuals with IGT have reconfirmed that these drugs also lower plasma glucose in nondiabetic individuals. In diabetes prevention trials, such glucose lowering by drugs has been called "the prevention of diabetes." Whether antidiabetes treatment can really be labeled as the prevention of type 2 diabetes requires a thorough discussion.

The pharmacologic effect of antidiabetes drugs on plasma glucose will gradually disappear after the drug use is discontinued, as shown by placebo-controlled trials with a cross-over design and studies using a "wash-out" period. Similarly, in recent diabetes prevention trials in individuals with IGT, the effect of metformin (8,10), acarbose (11), and troglitazone (12,13) began to disappear after relatively short wash-out periods. The Troglitazone in Prevention of Diabetes study in premenopausal women with previous gestational diabetes, however, reported (12) that troglitazone might have resulted in an improvement in insulin secretion in some women that remained even after the discontinuation of the drug. It is possible that this was due to the selection of the target population since in the DPP in older individuals with IGT such a long-lasting effect of troglitazone was not seen (13).

Recently, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial showed that the incidence of type 2 diabetes was 60% lower in individuals with IGT/impaired fasting glucose (IFG) when treated with rosiglitazone compared with placebo (14). This risk reduction was, as one may expect given the 1.6 mmol/l fall in 2-h post-challenge plasma glucose, 56% (95% CI 54–65%) (17). Thus, there was no additional effect on diabetes incidence over and above the glucose-lowering effect of rosiglitazone. Until today, the results from the wash-out period after the randomized treatment in the DREAM trial have not been published, but it would be surprising if glucose levels would not increase after stopping rosiglitazone.

DREAMS AND THE REALITY IN THE HOPE TO PREVENT THE ONSET OF DIABETES BY ACE INHIBITORS

— It has been suggested that action of ACE to increase angiotensin II and promote the breakdown of bradychinin may promote the development of diabetes, and that by inhibition of ACE and/or blockade of angiotensin II, the risk of diabetes may be reduced. The post-hoc analysis of the Heart Outcomes Prevention Evaluation study was the first placebo-controlled trial to suggest that the ACE inhibitor ramipril may prevent diabetes (18). Subsequently, additional post-hoc analyses of large controlled trials have also reported that ACE inhibitor use is associated with a lower incidence of diabetes in comparison with placebo or various active comparators (19). A growing number of post-hoc analyses from trials that used angiotensin II receptor blockers also suggest that they may have a similar effect (20). These trials were however not designed to test diabetes prevention as a primary hypothesis, and a proper diagnostic method (an oral glucose tolerance test) was not used, and most cases of diabetes were self-reported. Thus, it has remained unclear whether these drugs will really reduce the risk of diabetes.

The recent data from the DREAM trial in individuals with intermediate hyperglycemia have tested this hypothesis with the ACE inhibitor ramipril (21). The results were negative, i.e., ramipril did not reduce the incidence of diabetes compared with placebo, while this large trial clearly had the power to find a 20–25% effect that has been observed in previous post-hoc analyses (19). Next, we need to see whether angiotensin II receptor blockers will influence the risk of diabetes in placebo-controlled trials that are currently ongoing.

THE MYTH OF REVERTING TO "NORMOGLYCEMIA"

— It is obvious that antidiabetes drugs will bring plasma glucose levels of some indi-

viduals with IGT or IFG to a range that is considered normal. There is no trial that has attempted to maximally lower plasma glucose, and thus, claims about "reversion" are not appropriate. Regarding lifestyle trials where the aim has been to stop the progression from IGT to diabetes, the regression is not supported by the design. Nevertheless, in trials on serum LDL cholesterol and blood pressure, the statement "the lower the better" has been proven to be true. At present, for several biological parameters, the aim is to find the most adequate level, which is often close to that observed after birth.

SAFETY OF PREVENTIVE MEASURES

— For any treatment, the safety profile is very important, and similarly, measures to prevent diseases must be safe. To bring less harm compared with benefits is necessary for treatment. For preventive measures, an even stricter rule is needed; harm should be kept at minimum. Regarding pharmacologic and lifestyle interventions, there is a distinct difference in the potential regarding safety. Lifestyle interventions are safe, and they will typically promote healthy behaviors (diet, weight control, physical activity, etc.) that have multiple health benefits beyond diabetes prevention. Thus, the risk-to-benefit ratio of lifestyle intervention may be more favorable than what a single outcome assessment such as plasma glucose may indicate. While some drugs are known or believed to have multiple (pleiotropic) effects, modern drug development attempts to design drugs that have a specific target and mode of action. Pharmacologic interventions, on the other hand, often result in undesired effects that may increase with increasing dose of the drug. These may reduce the risk-to-benefit ratio of a drug and reduce the compliance with such an approach for long-term prevention of type 2 diabetes. For instance, significant weight gain associated with rosiglitazone in the DREAM trial (14) clearly works against the lifestyle advice to lose weight given to high-risk subjects and will place the individual in a very difficult situation.

ECONOMICS OF PREVENTION

— Cost-effectiveness or cost-benefit estimates of various interventions to prevent chronic diseases play an important role when deciding about their applicability for large-scale implementation. Important but rather limited information about cost-effectiveness of preventive measures can be derived from data collected during prevention trials. The conclusion of the DPP investigators was that preventive interventions were cost-effective and that lifestyle intervention was better than metformin (22). Metformin is one of the cheapest antidiabetes drugs and has relatively few side effects that are mostly mild. To use more recently developed drugs such as glitazones for prevention of diabetes would increase costs dramatically, while overall benefits might not increase in the similar degree, as seen in the DREAM trial.

The new follow-up data from the DPS will further strengthen the case of cost-effectiveness of lifestyle intervention for type 2 diabetes. After the intensive lifestyle intervention that was provided to the intensive intervention group for 4 years on average, additional benefits in terms of lower risk of type 2 diabetes were still obtained during at least 3 years without any effort from health personnel (15). This will improve the long-term cost-effectiveness estimates markedly. With pharmacologic intervention, such long-term effects after stopping the treatment are unlikely, and if treatment is continued for the long term, it will require efforts from health care providers in addition to the cost of the drug itself.

COMMUNITY-WIDE APPROACH TO PREVENT TYPE 2 DIABETES

— While it is obvious that a population-based strategy to fight the pandemic of type 2 diabetes is urgently needed, it is also evident that an individualized approach to guide people at high risk is warranted. A relatively simple lifestyle intervention seems to work well. However, further research is needed to reveal the optimal and most cost-efficient strategy, intensity, and duration of such an intervention. The results from the extended follow-up of the DPS nevertheless have demonstrated that the effect of lifestyle intervention on diabetes risk does not disappear after stopping active lifestyle counseling. This message is very important for planning and implementing community-based diabetes prevention programs. Antidiabetes drugs are nevertheless needed in such programs for the next stage, i.e., for effective pharmacotherapy to lower elevated blood glucose as early as possible to prevent deleterious effects of hyperglycemia.

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