EDITORIAL (SEE RETNAKARAN ET AL., P. 1601)

What's Next for Diabetes Prevention?

Recent estimates of the prevalence of diabetes and prediabetes underscore that no community is being spared from this ever-advancing, noncommunicable disease (1). Given that many individuals with these conditions are going to experience the long-term, ravaging outcomes of hyperglycemia, there is a continued and pressing need to develop approaches that will prevent the development and progression of diabetes as well as its micro- and macrovascular complications.

The last two decades have witnessed the introduction of a number of new classes of medications to treat diabetes and the refinement of others. We have also learned the benefits of more aggressive glucose lowering so that today interventions are frequently commenced earlier, and many patients are rapidly placed on more than a single agent. The focus on earlier intervention has also grown out of the recognition that the glucose elevation characterizing type 2 diabetes does not occur suddenly, but rather is a slow and progressive process with the pathophysiology well established at a time when the glucose levels have not yet reached the diagnostic thresholds (2). Thus, impaired glucose metabolism and diabetes represent a continuum and both are amenable to therapy.

Intervening to prevent the development of diabetes has been a focus of a number of studies over the last decade. In these, both lifestyle modification and medications have been used and have, in general, been successful in delaying the onset of the disease. Lifestyle modification reduces the risk of developing diabetes by over 50% (3,4), with different classes of medications having more variable impact (4–8). The greatest benefit from pharmacological intervention occurs with the thiazolidinediones (6–8), which have been shown to be as good, if not better, than lifestyle intervention.

In this issue of *Diabetes Care*, Retnakaran et al. (9) provide additional information about the effectiveness of pharmacologic intervention to prevent progression to diabetes from the Canadian Normoglycemia Outcome Evaluation (CANOE) Trial. The CANOE investigators treated individuals with impaired glucose tolerance with a low-dose combination of metformin and the thiazolidinedione rosiglitazone and demonstrated a reduction in the risk of developing diabetes (10), similar in magnitude to that seen with larger doses of thiazolidinedione monotherapy. The current report provides further information on glucose levels, insulin sensitivity, and β-cell function over the course of the study. As expected, glucose levels fell with combination therapy, the nadir being reached at 12 months, but thereafter they increased at a rate equivalent to that in the placebo group. This pattern is reminiscent of what was observed in the UK Prospective Diabetes Study (UKPDS) (11,12), and it was also observed in the Diabetes Prevention Program (DPP) with both the lifestyle and metformin interventions (4). However, it differs from what was reported in two large studies of diabetes prevention with thiazolidinediones (7,8) and in A Diabetes Outcome Prevention Study (ADOPT) in which rosiglitazone was compared with two other glucose-lowering agents, glyburide and metformin (13). In these latter three studies, progression of glycemia beyond a year was slower with thiazolidinedione therapy compared with either placebo or any of the active comparators (7,8,13), suggesting a possible modification of the underlying disease process.

As thiazolidinediones have been shown to be more durable than other agents, the finding in CANOE of a parallel increase in glucose levels on therapy compared with placebo is somewhat of a surprise. There are at least two possible explanations for this outcome using combination therapy. First, the dose of rosiglitazone used in this prevention study was less than the maximal dose, which was what was used when thiazolidinedione monotherapy was studied for diabetes prevention (7,8). Second, the effect of metformin in preventing progression to diabetes appears to be simply that of active glucose lowering as its prevention effect wanes rapidly after stopping the medication (14). Other explanations may also be offered, but at this time there is no clear answer.

Is it possible to truly prevent diabetes or is this just idealism? At this time, this has to continue to be the goal. Clearly, primary prevention by addressing societal issues related to obesity would be best, and we believe greater effort by authorities at the local, national, and international levels is needed and could stem the tide of obesity and with it diabetes. Further, for profit organizations need to make a concerted effort to put the health of the community at the forefront. This may seem somewhat idealistic, but we believe the lessons learned from tobacco cessation provide a foundation for a concerted multilevel effort (15).

In the meanwhile, we must also not lessen our efforts to find interventions that may truly prevent the progression from impaired glucose metabolism to diabetes. Such interventions should ideally halt the disease process so that after withdrawal, progression to diabetes no longer occurs. This goal would take us beyond what we already are able to achieve with lifestyle and thiazolidinediones that demonstrate an effect to delay the onset while treatment is ongoing, but do not totally halt disease progression. In the Finnish Diabetes Prevention Study (DPS), there was a legacy effect so that 3 years after stopping the lifestyle intervention, despite ongoing development of diabetes in subjects in both the intervention and control groups, the lifestyle group still exhibited a 43% reduction in relative risk (16). In the DPP and the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study, after discontinuation of the thiazolidinedione, there was again a lower cumulative incidence of diabetes in keeping with a legacy effect (6,17). However, the success with thiazolidinediones comes at a price with weight gain, edema, and increased risk of bone fractures (13,18). Thus, alternatives are needed. The recent development of incretin-based therapies and the successes observed in glucose lowering with bariatric surgery offer hope that true prevention may be possible.

Another aspect of the article by Retnakaran et al. raises an interesting question. How good are our assessments of insulin sensitivity and β-cell function? As with the flurry of new medications in the past 20 years or so, there has been a flood of new approaches to measure these parameters in order to gain better insight

into glucose metabolism. However, in many instances what these methods are estimating is unknown. They are often used in inappropriate circumstances and frequently have not been well validated. Let's consider a few examples.

1) A commonly used estimate is the insulinogenic index, which measures the early insulin response following nutrient ingestion. Little is known about how this measure relates to many others, and how it differs with glucose or a mixed meal, the latter where amino acid and incretin actions could be more influential.
2) The Homeostasis Model Assessment (HOMA) is widely used, frequently where there are small sample sizes and more technically demanding approaches would be more informative. Remembering that the HOMA equation for estimating insulin resistance was derived for use in fasting humans, it is not simply transferable to studies in rodents or to dynamic changes during a glucose tolerance test (19)!
3) Many different indices have been introduced and applied without any knowledge of whether they perform similarly in individuals with normal glucose tolerance or abnormal glucose tolerance or whether they are applicable when glucose-lowering medications are present. Is that the reason why even though both metformin and thiazolidinediones have been shown to improve insulin sensitivity and β-cell function in humans, Retnakaran et al.'s study failed to demonstrate an improvement in β-cell function (9), or why in ACT NOW (Actos Now for Prevention of Diabetes), there was a failure to demonstrate the expected improvement in insulin sensitivity (8)? We would suggest that a reappraisal of the approaches that are used and their application in a technically precise manner is necessary if we are going to gain more insight into the approaches for preventing diabetes.

So what is next for diabetes prevention? It is clear that progression to diabetes is dependent on the ongoing loss of β-cell function and possible reductions in the number of β-cells. The basis for these changes remains unclear. Thus, continued investigation addressing cellular mechanisms determining β-cell function and loss is vital. Discoveries of β-cell genes associated with prediabetes and type 2 diabetes could well provide insights for discovery. Further, studies using functional genomics and pharmacogenomics could be helpful in developing approaches for preventing progression. While this work is going on, clinical studies need to continue. Whether incretin-based therapies may improve islet health with sustained benefit is something we need to learn sooner rather than later. Further, combinations aside from low doses of metformin and thiazolidinediones may prove superior in the long term. The excitement being generated by the observation of diabetes resolution with bariatric surgery may in time provide other novel approaches to test. Thus, there is a great deal to be learned and more work to be done so that we can be in a position to witness the retreat of this scourge of noncommunicable diseases.

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