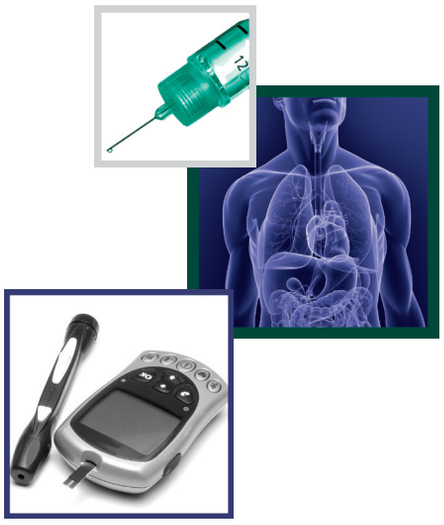
EDITORIAL

Can we prevent diabetes with a single pill?



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"...it is clear that drugs that both improve insulin sensitivity and augment/preserve β-cell function, such as pioglitazone ... are ideal agents for preventing the conversion of IGT to T2DM."

Type 2 diabetes mellitus (T2DM) has reached epidemic proportions in the USA and in Westernized countries. Approximately 29 million Americans have T2DM and approximately 70 million have prediabetes (impaired glucose tolerance [IGT] or impaired fasting glucose [IFG]). If left untreated, 40–50% of these prediabetic individuals will eventually progress to T2DM. Although diet and exercise are the initial choice for the treatment of IGT/IFG, they often fail and are difficult to maintain. It is well established that the microvascular, and to a lesser extent macrovascular, complications are closely related to the level of glycemic control (HbA1c). If the progression of IGT/IFG to T2DM can be prevented or delayed, then it is reasonable to expect that the microvascular complications of diabetes can be prevented/delayed. Therefore, if lifestyle intervention fails, individuals with IGT/IFG should be considered for pharmacologic therapy.

Before reviewing the therapeutic modalities for diabetes prevention, it is important to understand the underlying pathophysiologic abnormalities responsible for the development of T2DM. T2DM is characterized by two fundamental defects: impaired insulin secretion and insulin resistance in multiple tissues (muscle, liver and adipocytes). While defects in insulin action are present early in the natural history of the disease, overt diabetes does not occur until β-cell failure ensues [1]. Initially, in response to insulin resistance, the plasma glucose concentration is maintained within normal limits by a compensatory increase in insulin secretion. However, with time there is a progressive deterioration in β-cell function leading to the development of IGT/IFG and subsequently T2DM. Individuals with IGT are maximally/near-maximally insulin resistant and have lost a significant amount of β-cell function [1–2]. Thus, subjects in the upper tertile of IGT (2-h plasma glucose = 180–199 mg/dl) have lost approximately 70–80% of their β-cell function and have a significant reduction in β-cell mass [3].

Both lifestyle intervention and pharmacologic therapy have been shown to decrease the conversion of IGT/IFG to T2DM. In the Malmo prospective study, lifestyle modification led to a marked improvement in glucose tolerance in individuals with IGT and reduced progression to T2DM by 60% [4]. The largest study to examine the

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effect of lifestyle intervention was the Diabetes Prevention Progam (DPP) [5]. A total of 3234 IGT subjects were randomized to placebo, metformin or intensive lifestyle modification. After 2.8 years, the intensive lifestyle group had lost 7% of body weight and had a 58% reduction in the development of diabetes compared with the placebo group. After completion of the initial DPP study all participants were followed for additional 6.8 years in the DPPPOS study [6]. After a median follow up of 10 years, most of the lost weight had been regained in the lifestyle group but there still was a 34% reduction in development of diabetes compared with placebo. Similar results have been observed in the Finnish DPP.

If lifestyle modification is effective, why is pharmacologic therapy necessary for the treatment of IGT/IFG? The answer is simple: lifestyle modification is difficult to institute, is often ineffective, is even more difficult to sustain, and is expensive [7]. In the DPP, the participants were asked to consume a diet containing 1200–1800 kcal/day, had 16 sessions of dietary counseling and access to a dietician, had 150 min of supervised exercise per week, were assigned a personal trainer, and had a behavioral counselor. It is worth noting that these interventional strategies are not covered by traditional health insurance. Moreover, there was a 50% residual risk of diabetes despite this intensive lifestyle intervention and, even though an aggressive follow-up program was instituted, most subjects regained the majority of the lost weight. Therefore, even if one adopts a healthy lifestyle, pharmacotherapy will be required to prevent the development of T2DM in many individuals with IGT/IFG.

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Meformin has been shown to be effective in preventing the progression of IGT to T2DM in both the US [5] and Indian DPP [8]. In the US DPP, metformin, 850mg twice daily, reduced the development of diabetes by 31% compared with placebo [5]. Metformin was particularly effective in obese (BMI >35 kg/m^2) younger (<45 years) individuals, and in IGT subjects with a HbA1c >6.0%. Metformin therapy was associated with a weight loss of approximately 1.7 kg, which was maintained in the DPPOS extension and this was associated with an 18% reduction in the incidence of T2DM compared with the placebo group. Similar results with metformin have been reported in the Indian DPP [8].

In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) study, acarbose, an α-glucosidase inhibitor, reduced the conversion of IGT to T2DM by 25% compared with placebo. However, acarbose therapy was associated with a drop out rate of approximately 30% owing to gastrointestinal side effects, and poor patient acceptance has prevented this medication from achieving widespread use in clinical practice.

Studies involving insulin secretagogues for prevention of diabetes are limited. One recent study with nateglinide failed to show any benefit on preventing IGT conversion to T2DM [9].

The thiazolidinediones (TZDs) are potent insulin sensitizers and augment/preserve β-cell function [1]. In the DPP study, troglitazone decreased the conversion of IGT to T2DM by 75% before the drug was withdrawn because of hepatoxicity [10] and was superior to both metformin and lifestyle modification. In the DREAM study, rosiglitazone decreased the conversion of IGT to diabetes by 62% [11], but was associated with weight gain and a slightly higher incidence of fractures. Because of cardiovascular concerns, rosiglitazone has been removed from the European market and its use in the USA has been severely restricted. Pioglitazone has been shown to reduce the development of diabetes by 62% in women with history of gestational diabetes [12]. Importantly, in Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), pioglitazone reduced the composite cardiovascular end point by 10% ($p = 0.095$) and the MACE end point (death, myocardial infarction and stroke) by 16% ($p < 0.03$) [13]. A similar reduction in cardiovascular end points has been demonstrated with a meta-analysis of prospective studies carried out in the USA [14]. Furthermore, in T2DM, pioglitazone has been shown to slow the progression of carotid intima media thickness and coronary plaque accumulation [1].

The Actos Now Study for the Prevention of Diabetes (ACT NOW) randomized 602 individuals with IGT to pioglitazone or placebo. After a median follow-up period of 2.4 years, pioglitazone reduced the conversion rate to T2DM by 72% ($p < 0.00001$) and 48% of subjects treated with pioglitazone returned to normal glucose tolerance (NGT) compared with only 28% in the placebo group ($p < 0.001$) [15]. In addition, pioglitazone significantly decreased the blood pressure, reduced the plasma triglyceride concentration, increased the HDL-C and decreased the rate of increase in carotid intima-media thickness by 34%. The strongest predictor

of prevention of diabetes was the improvement in β-cell function, as measured with the insulin secretion/insulin resistance (disposition) index.

From the pathophysiological perspective it is clear that drugs that both improve insulin sensitivity and augment/preserve β-cell function, such as pioglitazone [1], are ideal agents for preventing the conversion of IGT to T2DM. Although similar beneficial effects of rosiglitazone on β-cell function and insulin resistance have been observed in DREAM [10], this TZD is no longer available because of potential cardiovascular side effects.

It has been argued that TZD therapy simply masks the presence of diabetes rather than preventing it, and the readers are referred to the excellent review of this topic by Buchanan [16]. Since IGT subjects treated with a TZD never catch up to the placebo-treated group after discontinuation of the TZD, we would argue that pioglitazone does modify the course of the disease. Most importantly, it is unreasonable to think that one can reverse the genetic basis of T2DM. Therefore, at some point after discontinuation of the TZD or any pharmacologic agent, one would expect the conversion rate of IGT to T2DM to increase. However, as long as the TZD therapy is continued and HbA1c levels remain within the normal range, one can fully expect that the microvascular complications of diabetes would be prevented. Therefore, we believe that IGT should be treated aggressively and early, rather than waiting for the complications of hyperglycemia to set in before initiating any therapy.

Side effects associated with pioglitazone include weight gain, fluid retention, congestive heart failure and fractures. As the side effects are dose–response related, they can largely be avoided by using lower doses of pioglitazone (15–30 mg/day) [17]. Paradoxically, the greater the weight gain, the greater the decline in HbA1c levels and the greater the improvements in insulin sensitivity and insulin secretion [1,18]. Fluid retention is readily detectable by the finding of pedal edema and is easily treated with distally acting diuretics. There is a small increase in fractures (adjusted hazard ratio: 1.57, 95% CI: 1.16–2.14) in postmenopausal women treated with pioglitazone [19]. These fractures involve the long bones of the arms and legs and are related to trauma. Bone mineral density should be quantitated prior to institution of TZD therapy in postmenopsual women. In the CANOE study low dose rosiglitazone (2 mg/day) plus metformin (1000 mg/day) reduced the conversion rate of IGT/IFG to T2DM by 66% ($p < 0.005$) without weight gain, fluid retention or bone fractures [20]. Based on this study, we believe that the ideal therapy for IGT would be low dose pioglitazone (15–30 mg/day) plus metformin (1000 mg/day).

In a recent study, liraglutide in obese subjects was shown to be very effective in promoting weight loss [21]. Approximately a third of these obese individuals had IGT and, in this subgroup, liraglutide reverted IGT to NGT by 86–94%. Similarly, exenatide has been shown to be effective in preventing the progression of IGT to T2DM and in promoting reversion to NGT [22]. Thus, the long-acting GLP-1 analogs are likely to be very effective and patient friendly for the treatment of IGT since they have a potent effect to preserve β-cell function [1,23].

In the future, it is likely that we will have novel drugs that more effectively correct the basic pathophysiologic defects (impaired insulin secretion and insulin resistance) present in IGT/IFG with fewer side effects. However, currently, of the available drugs, low-dose pioglitazone (15–30 mg/day) plus low-dose metformin (500–1000 mg/day), added to lifestyle intervention, are the most effective interventions for the progression of IGT to T2D.

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Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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