EXPERT OPINION

What are the pharmacotherapy options for treating prediabetes?

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Introduction: The incidence of type 2 diabetes mellitus (T2DM) has risen to epidemic proportions, and this is associated with enormous cost. T2DM is preceded by 'prediabetes', and the diagnosis of impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) provides an opportunity for targeted intervention. Prediabetic subjects manifest both core defects characteristic of T2DM, that is, insulin resistance and β-cell dysfunction. Interventions which improve insulin sensitivity and/or preserve β-cell function are logical strategies to delay the conversion of IGT/IFG to T2DM or revert glucose tolerance to normal.
Areas covered: The authors examine pharmacologic agents that have proven to decrease the conversion of IGT to T2DM and represent potential treatment options in prediabetes.
Expert opinion: Weight loss improves whole body insulin sensitivity, preserves β-cell function and decreases progression of prediabetes to T2DM. In real life long-term weight loss is the exception and, even if successful, 40 – 50% of IGT individuals still progress to T2DM. Pharmacotherapy provides an alternative strategy to improve insulin sensitivity and preserve β-cell function. Thiazolidinediones (TZDs) are highly effective in T2DM prevention. Long-acting glucagon-like peptide-1 (GLP-1) analogs, because they augment β-cell function and promote weight loss, are effective in preventing IGT progression to T2DM. Metformin is considerably less effective than TZDs or GLP-1 analogs.

Keywords: glucagon-like peptide-1 analogs, pharmacotherapy, prediabetes, weight loss

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a common condition and represents a serious and continuously expanding global health problem. Three hundred and eighty-two million people, or 8.3% of adults, worldwide are estimated to have diabetes and by 2035, ~ 592 million people, or 1 in 10 adults, will have diabetes [1].

The Diabetes Control and Complications Trial [2], the United Kingdom Prospective Diabetes Study (UKPDS) [3,4], and the Kumamoto Study [5] have documented that hyperglycemia is the major risk factor for microvascular and, to lesser extent, macrovascular [6,7] complications. Recent clinical trials have provided evidence that tight glycemic control is less effective in preventing diabetes macrovascular complications in subjects with longstanding, poorly controlled T2DM than in individuals with new onset diabetes [8,9]. Because most of the morbidity and mortality in T2DM arises from long-term complications, early detection and effective intervention would be expected to have enormous beneficial medical, social and economic impact. Recent evidence has reinforced the T2DM approach attempting to prevent the disease by prediabetes treatment. Prospective epidemiologic studies [10-12] have demonstrated that the natural history of T2DM evolves from normal glucose tolerance (NGT) to 'prediabetes' to T2DM. Further, the core pathophysiologic disturbance insulin resistance and progressive β-cell failure responsible for prediabetes (impaired glucose tolerance [IGT] and impaired fasting glucose

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Article highlights.

- Individuals with prediabetes already manifest in moderate-severe form the core pathophysiologic defects (insulin resistance in muscle/liver and impaired insulin secretion) that are characteristic of type 2 diabetes mellitus (T2DM).
- Because hyperglycemia is the principal factor responsible for the development of microvascular complications, it logically follows that intervention at the prediabetic stage to prevent the development of hyperglycemia will prevent/delay the onset of retinopathy, nephropathy, and neuropathy.
- Lifestyle intervention is effective in preventing the development of T2DM in prediabetic individuals. However, weight regain is common and 40 – 50% of prediabetic individuals progress to T2DM despite successful weight loss.
- Pharmacologic therapy with a variety of antidiabetic agents (pioglitazone, metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, α glucosidase inhibitors) has proven effective in preventing the conversion of prediabetes to T2DM.
- Combined low-dose pioglitazone (15 – 30 mg/day)/ metformin (1.0 – 1.5 g/day) and GLP-1 receptor agonists are particularly effective in preventing the conversion of prediabetes to diabetes and are associated with minimal side effects.
- Metformin has been shown to be cost effective in the diabetes prevention program (DPP) study and it is likely that generic pioglitazone also will prove to be cost-effective, making combined low-dose pioglitazone plus metformin an especially attractive approach to treating individuals with prediabetes.

This box summarizes key points contained in the article.

[IFG]) are the same ones responsible for dysregulation of glucose metabolism in T2DM [13-15]. Since the microvascular complications of diabetes are related to both the severity and duration of hyperglycemia, it logically follows that early pharmacologic intervention at the stage of prediabetes and maintenance of hemoglobin A1c (HbA1c) in the nondiabetic range will have a major impact to reduce these devastating complications. Moreover, pharmacologic intervention at the prediabetic stage has that potential to prevent/slow the progressive loss of β-cell mass that is characteristic of T2DM [16].

No long-term, prospective clinical trial has examined whether prevention of the conversion of prediabetes T2DM is associated with a decrease in the risk of microvascular or macrovascular complications. However, it is likely that prevention of diabetes in prediabetic individuals will be associated with decreased microvascular risk for the following reasons: i) it is universally accepted that hyperglycemia is the major risk factor responsible for the development of microvascular complications [3-5,17]. Thus, it logically follows that prevention of hyperglycemia (i.e., T2DM) will prevent the development of microvascular complications; ii) the relationship between microvascular risk and HbA1c is a continuum with no threshold above which the microvascular risk is not increased, and the microvascular risk increases curvilinearly as HbA1c exceeds ~ 6.0% [6,18-20]. Thus, maintaining HbA1c < 6.0% is likely to prevent the development of microvascular complications; iii) in the diabetes prevention program (DPP) study [21], 8.0% of participants already had evidence for retinopathy before entering the study even though the mean HbA1c was 5.8%. Further, the prevalence of retinopathy in IGT individuals who developed diabetes increased to 12%, suggesting that the conversion of IGT to T2DM is associated with increased risk of retinopathy; and iv) in the Da Quing study [22], subjects who received lifestyle intervention had a 50% decrease in the conversion of IGT to T2DM and the decrease in T2DM incidence was associated with a 60% decrease in the incidence of blindness and laser therapy at 20 years of follow-up. Based on the above discussion, we believe that it is very likely that prevention of the conversion of prediabetes to T2DM will be associated with decreased microvascular risk. Since glycemia (HbA1c) is a weak risk factor for macrovascular complications, it is more speculative as to whether improved glycemic control *per se* will reduce the incidence of myocardial infarction and stroke.

2. Definition of prediabetes

According to the American Diabetes Association, the diagnosis of prediabetes is made on the basis of one of the following: i) 2-h plasma glucose (PG) during oral glucose tolerance test (OGTT) = 140 – 199 mg/dl (IGT); ii) fasting plasma glucose (FPG) = 100 – 125 mg/dl (IFG); and iii) HbA1c = 5.8 – 6.4% [23]. It should be emphasized that the progression from NGT to IGT/IFG to T2DM is a continuum [24-26], and the cut off points established by the ADA are quite arbitrary and are not based upon the underlying pathophysiology. As we have shown, individuals with IGT and a 2-h glucose in the upper half (170 – 199 mg/dl), that is, HbA1c = 6.0 – 6.4%, already are maximally/near maximally insulin resistant and have lost over 80% of their β-cell function. We would argue that such individuals already have diabetes and should receive pharmacologic therapy aimed at reversing core pathophysiologic defects in order to prevent progression of the disease and worsening hyperglycemia.

Although subjects with isolated IFG and isolated IGT have a similarly increased risk for future T2DM, epidemiological studies have reported only partial overlap between the prevalence of the two states. Importantly, future T2DM risk combined with IFG/IGT is twofold greater compared with subjects with either state alone [27-32]. Initiation of treatment in IGT, IFG or IGT/IFG individuals with interventions that reverse-specific pathophysiologic defects present in the prediabetic state [24,26,33-35] provides a promising strategy to prevent development of hyperglycemia and its associated vascular complications.

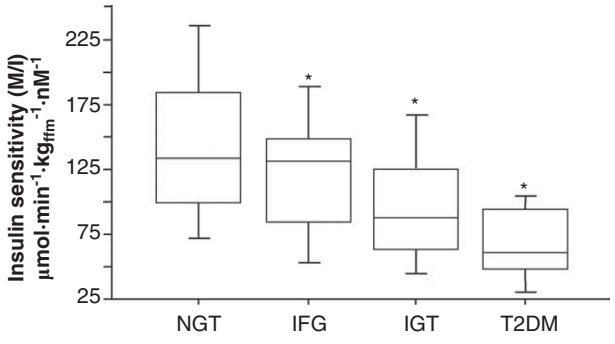

Figure 1. Insulin sensitivity (box plot of M/I) in individuals with NGT, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM).
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*Indicate a significant difference from the NGT group.
NGT: Normal glucose tolerance.

3. Metabolic abnormalities in prediabetes and overt type 2 diabetes

The FPG is tightly regulated and in NGT individuals rarely exceeds 90 mg/dl, while the 2-h postmeal glucose usually is < 120 mg/dl [36]. Knowledge of the pathophysiologic mechanisms responsible for prediabetes and overt T2DM provides a rational basis for the choice of pharmacological agents for T2DM prevention.

3.1 Insulin resistance

Insulin resistance is a core defect in both prediabetes and T2DM [13-15,24,33,37-43], involves liver [13-15,41,43], muscle [13-15,40,42,43] and adipose tissue [15], and precedes the development of glucose intolerance and overt T2DM (**Figure 1**) [13-15,24,26,34,35,44,45]. IFG individuals have moderate hepatic insulin resistance and impaired early insulin response (0 – 30 min) during the OGTT [24,33,34,46-49]. As such, they are characterized by elevated FPG and an excessive early rise (0 – 60 min) in PG during OGTT. However, because the late plasma insulin response (60 – 120 min) is intact and muscle insulin sensitivity is normal/near-normal, the 2-h PG returns to its starting FPG level.

In contrast, IGT individuals have moderate-severe muscle insulin resistance and impaired early (0 – 30 min) and late (60 – 120 min) plasma insulin responses during the OGTT [24,33,34,47-49]. Thus, although FPG is not elevated, there is a progressive, sustained rise in PG during OGTT and 2-h PG remains well above the FPG level. Impaired first-phase insulin secretion is characteristic of both IGT and IFG. However, they are distinguished by intact second-phase insulin secretion in IFG and the tissues (liver in IFG vs muscle in IGT) responsible for insulin resistance. In IGT skeletal muscle is the main tissue responsible for impaired insulin-mediated glucose uptake [24,33-35]. Adipose tissue also is resistant to insulin-stimulated glucose disposal, but its contribution to whole body glucose disposal is small compared to muscle [50]. However, adipocytes are resistant to the antilipolytic effect of insulin [43] and the elevated plasma FFA levels cause insulin resistance in muscle and liver [51] and impair β-cell function [52].

3.2 β-cell dysfunction

Although insulin resistance is a cardinal feature of IGT, ultimately β-cell failure is responsible for development of IGT and its progression to T2DM (**Figure 2**) [24,26,34,35,44,53-56]. In all ethnic groups, low plasma insulin response during OGTT and impaired first-phase insulin secretion (0 – 10 min time period) following intravenous glucose are strong predictors of IGT progression to T2DM [24,26,34,35,48,53,54,56-58]. When FPG exceeds 90 – 100 mg/dl, first-phase insulin secretion begins to deteriorate, and, when FPG exceeds 110 mg/dl, first-phase insulin secretion is almost completely lost [13-15,56-58]. Genetic [13,15,53,54] and acquired factors (glucotoxicity [59], lipotoxicity [60], incretin deficiency/resistance [61-64]) play a major role in the progressive deterioration of β-cell function. Individuals in the upper half of IGT (2-h PG = 170 – 199 mg/dl) are maximally/near maximally insulin resistant and have lost ~ 70 – 80% of their β-cell function [24,33,34]. Thus, a small further decline in insulin secretion will result in a marked increase in fasting/postprandial blood glucose levels. Therefore, pharmacologic interventions that prevent/delay the decline in β-cell function can be expected to prevent/delay the progression of IGT to T2DM.

4. Diabetes prevention: therapeutic options

4.1 Do lifestyle interventions have sustained effects?

Obesity is an insulin-resistant state and represents the single most important risk factor for progression of IGT to diabetes [15,37,38,45]. By causing insulin resistance obesity, together with physical inactivity, places an increased insulin secretory demand on pancreatic β-cells. Lifestyle intervention, when successful, is effective in reducing IGT progression to T2DM by improving insulin sensitivity and augmenting β-cell function [65-72]. However, the great majority of individuals regain the lost weight in 2 – 3 years [73-76]. This is demonstrated graphically in the DPP (**Figure 3**) [70]. This indicates the lack of 'legacy' effect of weight loss on prevention of IGT progression to T2DM. Moreover, attempts to translate DPP results to 'real world' clinical practice and achieve a 5% weight loss have proven difficult. In a community study in Finland [77] 10,149 high-risk individuals were enrolled in a diabetes prevention program designed to achieve 5 – 7% body weight loss. Only one-third of participants successfully reduced their body weight by > 2.5%. Moreover, weight loss, even when achieved, is effective in decreasing the incidence of diabetes by only 50 – 60% [67]. Therefore, 40 – 50% of IGT subjects still progress to T2DM despite successful weight loss, indicating that lifestyle intervention alone is insufficient to prevent diabetes in a large percentage of

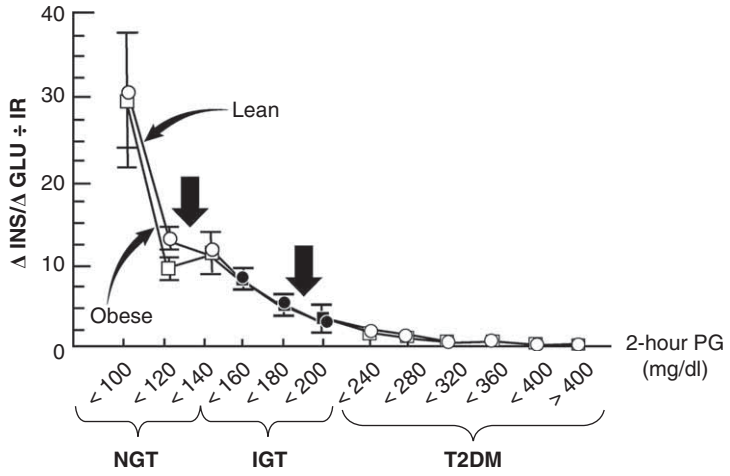

Figure 2. Insulin secretion/insulin resistance (disposition) index (defined as increment in insulin/increment in glucose ÷ insulin resistance [ΔINS/ΔGLU ÷ IR]) in individuals with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) as a function of the 2-h plasma glucose (PG) concentration in lean (closed circles) and obese (open circles) subjects.

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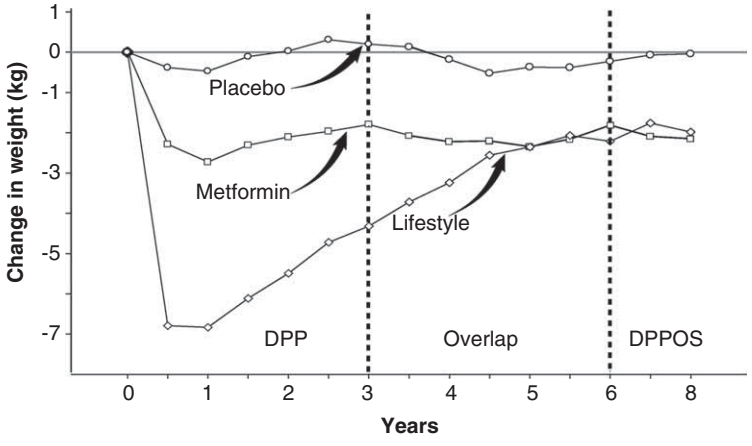

Figure 3. Change in body weight during the DPP, during the overlap period, and during the DPP Outcomes Study (DPPOS).

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DPP: Diabetes prevention program.

individuals. In contrast to behavioral modification (diet plus exercise), pharmacological therapy uniformly reduces IGT/IFG conversion to T2DM.

4.2 Reversal of insulin resistance by pharmacological therapy

4.2.1 Weight loss

In simplest terms, obesity results from energy intake greater than energy expenditure. Genetics, environmental and cultural factors all contribute to the development of obesity [78]. Three mechanisms have been exploited to promote negative energy balance: inhibition of nutrient absorption, appetite suppression and increased energy expenditure.

Orlistat reversibly inhibits human gastrointestinal lipases and effectively blocks absorption of ~ 30% of fat contained in the meal [79]. In XENDOS, orlistat caused a 2.8 kg greater weight loss compared to lifestyle intervention (5.8 vs 3.0 kg) and was associated with a 37% decrease in IGT progression to T2DM [80]. Several classes of medications have been shown to cause weight loss by suppressing appetite: sympathomimetics, serotonergics, endocannabinoid antagonists and others. Rimonabant, a selective blocker of cannabinoid CB1 receptors [81], was investigated in the Rimonabant in Obesity (RIO) trial [82] to assess the drug's effect on development of diabetes in obese prediabetic individuals [83]. Significant reductions in fasting plasma insulin and HOMA-IR and a greater percentage of

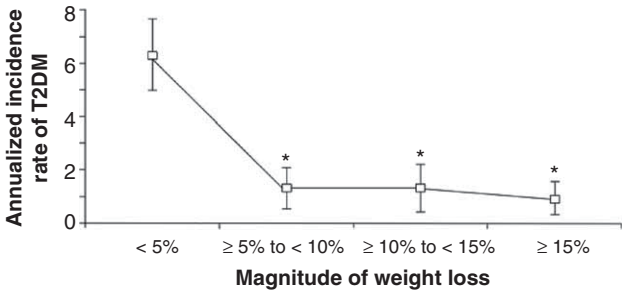

Figure 4. Relationship between weight loss and type 2 diabetes incidence at study end in the cohort of subjects with prediabetes and/or metabolic syndrome. Error bars represent 95% CI. Annualized incidence rate of type 2 diabetes was based on first occurrence of two consecutive fasting glucose values ≥ 7.0 mmol/l, two consecutive 2-h plasma glucose values during OGTT ≥ 11.1 mmol/l or taking antidiabetic medications at end point.

*p < 0.05 versus < 5% weight loss for all comparisons.

T2DM: Type 2 diabetes mellitus.

IFG patients whose fasting glucose level became normal were observed in rimonabant versus placebo group. However, similar to lifestyle intervention, weight loss induced by pharmacologic therapy is followed by weight regain when drug therapy is replaced by placebo, despite continued dietary intervention [82]. Rimonabant was withdrawn from the market in 2008 due to its psychiatric side effects [84]. However, development of CB1 receptor antagonists has not yet been abandoned and brain non-penetrant CB1 receptor antagonists that act only at peripheral sites might prove to be a promising therapeutic approach for inducing weight loss in obese individuals.

Co-administration of phentermine and topiramate extended-release induces significant weight loss in overweight/obese adults [85,86]. Phentermine is a sympathomimetic agent that stimulates release of norepinephrine and acts in the central nervous system to suppress appetite and reduce caloric intake. Topiramate is FDA-approved for treatment of seizures and also suppresses appetite, although its mechanism of action is unknown. In the CONQUER study phentermine/topiramate reduced body weight by 9.8% in overweight/obese adults with ≥ 2 weight-related comorbidities over 56 weeks. In a 52-week blinded extension study, SEQUEL, phentermine/topiramate reduced progression of prediabetes to T2DM by 71 and 79% in patients treated with 7.5/46 and 15/92 mg, respectively, compared with placebo over 108 weeks (**Figure 4**) [87]. The ability to prevent T2DM was closely related to the magnitude of weight loss and as previously demonstrated by Diabetes Prevention Program [67], Finnish Diabetes [66] and Da Qing studies [72]. Additional studies are needed to determine whether weight loss associated with phentermine/topiramate treatment will be maintained beyond 2 years and lead to sustained lower rates of progression to T2DM.

The glucagon-like peptide (GLP)-1 receptor agonists are potent appetite suppressants and markedly reduce the progression of IGT/IFG to T2DM. Because they exert other important effects (increased insulin and decreased glucagon secretion; suppression of hepatic glucose production), their role in diabetes prevention will be discussed in a later section.

No agent that safely increases thermogenesis (basal metabolic rate) is available. The mechanism of weight loss with sibutramine has been related to both decreased appetite and increased energy expenditure [88], but no study has assessed whether this agent can delay or prevent T2DM in prediabetes individuals.

4.2.2 *Metformin*

Metformin reduces FPG concentration and HbA1c in T2DM [89,90] by inhibiting hepatic glucose production [89-91]. In some studies, metformin also has been shown to improve muscle insulin sensitivity [92], although this effect most likely is related to weight loss (metformin is an appetite suppressant and causes gastrointestinal side effects) and not to a direct muscle insulin sensitizing effect [91]. Metformin does not stimulate insulin secretion [89] or preserve β-cell function, [93], and, as demonstrated in UKPDS, ADOPT and other studies [4,94,95] after an initial decline HbA1c rises progressively in metformin-treated T2DM patients. In DPP, metformin (1700 mg/day) reduced IGT conversion to T2DM by 31% [67] in association with improved weight loss and insulin sensitivity [96]. In young (< 65 years) obese (body mass index [BMI] > 35) subjects with IFG, metformin was as effective as weight loss in decreasing IGT progression to T2DM [67] and promoted regression to NGT in 40% of IGT individuals with BMI > 30 kg/m^2 [97]. Metformin also reduced IGT conversion to T2DM in Indian DPP [68]. In the Chinese Diabetes Prevention Study (CDPS) [98], metformin reduced IGT conversion to T2DM by 77% compared with the control group over 3 years. In both groups, BMI was ~ 25 kg/m^2, which is of interest considering the important role of obesity in the progression to overt T2DM. On the basis of these studies, ADA Consensus Conference recommended that high-risk individuals (HbA1c ≥ 6.0%; BMI ≥ 30 kg/m^2; age ≤ 60 years) with IGT or IFG be treated with metformin [23] due to the drug's long-term safety record. However, metformin, like sulfonylureas [3,4], does not prevent the progressive β-cell failure that is characteristics of T2DM, and it is not surprising that metformin (with the exception of the small Chinese study) is considerably less effective than thiazolidinediones (TZDs) and GLP-1 receptor agonists, which have potent beneficial effects on β-cell function, in preventing progression of prediabetes to diabetes (**Table 1**).

4.2.3 *Thiazolidinediones*

TZDs are powerful insulin sensitizers in muscle, liver, adipocytes [15,99-104] and augment and preserve β-cell function on a long-term basis [16,83,102,105,106]. TZDs act via the

Table 1. Summary of pharmacologic intervention trials in individuals with prediabetes.

Study	Ref.	Number of subjects studied	Intervention	Comparator	Duration (years)	Incidence of T2DM in controls (%)	Relative risk reduction (%)
IDPP	[68]	269	Metformin	No comparator	2.5	18.3	26
US DPP	[67]	2151	Metformin	Placebo	2.8	11	31
US DPP	[107]	1172	Troglitazone	Placebo/ metformin	0.9	11	75
TRIPOD	[102]	236	Troglitazone	Placebo	2.5	13.1	55
DREAM	[109]	5269	Rosiglitazone	Placebo	3	6.5	60
ACT NOW	[16]	602	Pioglitazone	Placebo	2.8	6	70
CANOE	[116]	207	Rosiglitazone and metformin	Placebo	3.9	10.1	66
STOP NIDDM	[132]	1368	Acarbose	Placebo	3.2	8.1	36
Ph-3 STUDY GROUP	[133]	1778	Voglibose	Placebo	3.0	12	40
XENDOS	[80]	3305	Orlistat	Placebo	4.0	2.2	37
SEQUEL	[87]	316	Phentermine/ topiramate 7.5/46 or 15/92 mg	Placebo	2.3	3.5	49 (7.5/46) 88 (15/92)
NN8022-1807 STUDY GROUP	[125]	169	Liraglutide (1.2→3.0 mg)	Placebo/orlistat	0.4	0.01	84 – 96

PPAR-γ [9] to improve insulin sensitivity by multiple mechanisms. TZDs inhibit lipolysis, reduce plasma-free fatty acid levels, increase fatty acid oxidation, reduce intramyocellar levels of toxic lipid metabolites (FARoAs, diacylglycerol, ceramides) redistributing fat from visceral to subcutaneous adipose depots [15,60,103]. A direct insulin-sensitizing effect mediated via PPAR-γ receptor in muscle and adipocytes also has been demonstrated [5,60,103]. All three TZDs troglitazone [99], pioglitazone [100] and rosiglitazone [101] similarly improve insulin sensitivity and glycemic control in T2DM. In IGT individuals and women with history of gestational diabetes [102], troglitazone enhances insulin sensitivity, improve glucose tolerance and decrease the progression of IGT to T2DM. In DPP, troglitazone reduced IGT conversion to diabetes by 23% after 3 years, although the drug was discontinued after a mean of 10 months because of liver toxicity [107]. During the initial 15 years, when IGT subjects actively were taking troglitazone, the diabetes incidence (3.0 cases/100 person-treatment years) was markedly reduced compared with placebo (12.0), metformin (6.7) and lifestyle intervention (5.1) groups, respectively. Two small studies in overweight/obese IGT individuals demonstrated that rosiglitazone 4 mg/day caused 33% regression to NGT that increased to 44% when rosiglitazone was escalated from 4 to 8 mg/dl [108]. In DREAM, rosiglitazone reduced IGT conversion to T2DM by 62% [109], and improvement in β-cell function insulin secretion/insulin resistance index was the best predictor of diabetes prevention. In women with history of gestational diabetes mellitus, both troglitazone in the prevention of diabetes and pioglitazone in the prevention of diabetes markedly reduced IGT progression to T2DM by 50 and 52%, respectively [102,105]. In ACT NOW [16], pioglitazone decreased by 72% ($p < 0.00001$) the conversion rate of IGT to T2DM over a 2.4-year follow-up period, and 48% of IGT individuals reverted to NGT. Pioglitazone improved insulin sensitivity by 92%, but the strongest predictor of diabetes prevention/final glucose tolerance status was β-cell function (insulin secretion/insulin resistance or disposition index) (**Figure 5**) [110].

4.3 Preservation of β-cell function

4.3.1 Pleiotropic effects of TZDs

Progressive β-cell failure is the principal factor responsible for IGT progression to T2DM. Although TZDs markedly improve insulin sensitivity in IGT individuals, enhanced β-cell function is the strongest predictor of T2DM prevention [110]. Studies in diabetic humans [106] and animals [111] demonstrate that troglitazone [102], pioglitazone [106,112] and rosiglitazone [106,109] augment β-cell function by multiple mechanisms: i) improved insulin sensitivity, with unloading of β-cells; ii) decrease in plasma-free fatty acid concentration; iii) mobilization of toxic lipid metabolites (fatty acyl CoAs, diacylglycerol and ceramides) out of β-cells (reversal of lipotoxicity); iv) direct β-cell effect mediated via the PPAR-γ receptor; and v) increase in insulin sensitizing adipocytokines (adiponectin) and decrease in insulin antagonistic adipocytokines (TNF-α) [15,104,113]. Because TZDs preserve both β-cell function and improve insulin sensitivity, they are very effective in preventing IGT progression to T2DM and producing durable HbA1c reduction in T2DM [15,16]. However, because of fat weight gain, fluid retention and cost [107-109], the ADA Consensus statement recommended metformin, not TZDs, for treatment of IGT/IFG [23], although TZDs

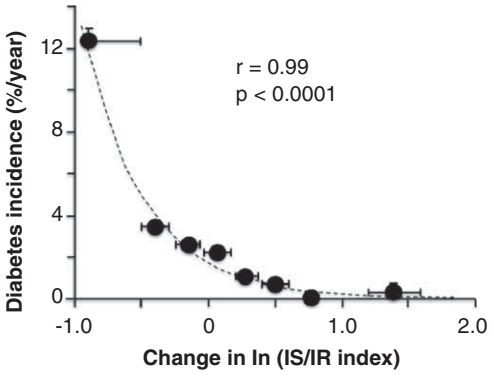

Figure 5. Relationship between the annual diabetes incidence rate and the change in the ln of insulin secretion (IS)/insulin resistance (IR) index in the combined pioglitazone- and placebo-treated individuals.

consistently have been at least twice as effective as metformin in reducing IGT conversion to T2DM. Of note, the greater the weight gain, the greater is the reduction in HbA1c [114] and fluid retention responds well to distally acting diuretics, that is, spironolactone. In ACT NOW [16], the pioglitazone dose was titrated to 45 mg/day. However, lower doses (15 – 30 mg/day) improve insulin sensitivity and insulin secretion in T2DM [112] and are associated with less weight gain and fluid retention [115]. In native Canadians with IGT [116], low-dose rosiglitazone (4 mg/day) plus metformin (1000 mg/day) reduced IGT conversion to T2DM by 71% without weight gain or fluid retention.

TZDs have been shown to decrease and maintain a durable reduction in HbA1c in T2DM subjects in eight of eight long-term (≥ 1.5 years) studies [15]. In ADOPT, HbA1c decrement with rosiglitazone was maintained for 5 years [94]. This sustained HbA1c reduction is explained by the TZD's long-term effect to preserve β-cell function [15,16,106]. Consistent with this, pioglitazone and rosiglitazone similarly increased β-cell function, measured with the gold standard insulin secretion/insulin resistance index [106]. In summary, in addition to their insulin-sensitizing effect, TZDs improve and preserve β-cell function, cause a durable HbA1c reduction in T2DM, and markedly reduce IGT conversion to T2DM.

4.3.2 Incretins: a novel target for diabetes prevention

4.3.2.1 GLP-1 analogs

Following oral glucose administration, the plasma insulin response is 2 – 3-fold greater than with intravenous glucose [64]. This incretin effect is explained by release of two gastrointestinal hormones: GLP-1, released by L cells, and glucose-dependent insulinotropic polypeptide (GIP), released by K cells, which together account for 90% of the incretin effect [64,117]. Both GLP-1 and GIP are potent insulin secretagogues. In addition to augmenting insulin secretion, GLP-1 also inhibits glucagon secretion, delays gastric emptying and promotes weight loss by suppressing appetite and decreasing food intake. Because native GLP-1 and GIP are rapidly cleaved (half-life = 1 – 2 min) by dipeptidyl peptidase-4 (DDP-4), both peptides are inappropriate for therapeutic use in T2DM and IGT subjects. Liraglutide and exenatide are GLP-1 receptor agonists that mimic the actions of GLP-1 and are resistant to DDP-4 degradation. Similar to endogenous GLP-1, both agonists are potent insulin secretagogues, inhibit glucagon secretion, promote weight loss and effectively reduce PG levels in T2DM [64,117-122]. In a long-term (3 years) extension study, exenatide produced a durable HbA1c reduction, improved β-cell function and caused progressive weight loss in T2DM individuals [119]. Hypoglycemia is uncommon with GLP-1 analogs because they only augment insulin secretion in the presence of hyperglycemia.

Glucose stimulates insulin secretion by increasing production ATP leading to closure of the ATP-dependent potassium channel. This causes depolarization of β-cell membrane followed by calcium influx, which triggers exocytosis of insulin-containing vesicles [123]. Both GLP-1 and GIP mediate their β-cell effects via a mechanism that is distinct from hyperglycemia. Following binding to their respective receptors, GLP-1 and GIP activate adenylate cyclase, which converts ATP to cAMP, which 'amplifies' an insulin secretory system that has been already activated by hyperglycemia [121]. In the absence of hyperglycemia, neither GLP-1 nor GIP increases insulin secretion. Subjects with IGT and T2DM are characterized by severely impaired β-cell function and markedly reduced incretin effect in response to meal/glucose ingestion [64]. Thus, GLP-1 analogs represent logical candidates for type 2 diabetes prevention. Studies from our group and others have demonstrated that the primary defect in IGT and T2DM is an inability of the β-cell to respond to glucose [26,34], and this β-cell 'blindness' to glucose, at least in part, can be restored by incretin hormones [120]. In IGT, most studies have reported no change or slightly impaired total GLP-1 response to a mixed meal [64], although the early (0 – 10 min) GLP-1 response is diminished, indicating a phasic defect in GLP-1 secretion; GIP secretion is normal or slightly increased [64]. In contrast, marked β-cell resistance to the stimulatory effect of both GLP-1 and GIP on insulin secretion is well documented in T2DM [61-64,120]. β-cell sensitivity to GIP, unlike GLP-1, can be restored after normalization of glycemia with insulin [62]. Although T2DM patients fail to respond to a physiologic increase in GLP-1 concentration [61-63,120], if the GLP-1 infusion is increased to cause a pharmacological rise in plasma GLP-1, a normal insulin response to the hyperglycemic stimulus is achieved (**Figure 6**). These results indicate that pharmacological levels of plasma GLP-1 are capable of correcting β-cell 'blindness' to glucose and restoring a normal β-cell response to glucose in IGT and T2DM. Although the stimulatory effect of GLP-1 analogs on β-cell function wane rapidly upon washing out the drug, a recent study reported that, if exenatide is continued

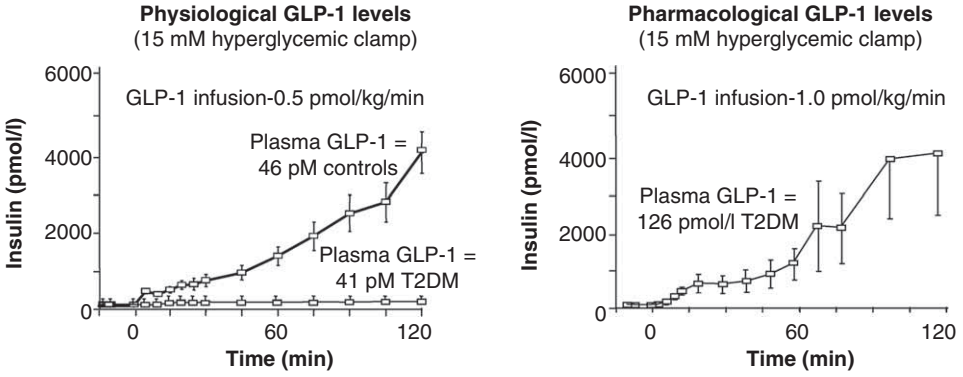

Figure 6. Effect of physiologic (left) and pharmacologic (right) doses of GLP-1 on insulin secretion in NGT individuals and in subjects with T2DM.

Reproduced from [62].

GLP-1: Glucagon-like peptide-1; NGT: Normal glucose tolerance; T2DM: Type 2 diabetes mellitus.

for 3 years, its ability to enhance β-cell responsiveness to glucose is partially retained [120].

4.3.2.2 *Evidence from clinical trials*

Because relentless β-cell failure is responsible for progression from NGT to IGT to T2DM (**Figures 1** and **2**) [13-15,26,35,53] and because GLP1 receptor agonists (exenatide and liraglutide): i) improve β-cell function in subjects with T2DM; ii) promote weight loss by reducing appetite and food intake; iii) do not cause hypoglycemia; and iv) can be given once weekly (Bydureon™) or once daily (Victoza), they are ideal agents for decreasing progression of IFG/IGT to T2DM and reverting glucose tolerance to normal. In a recent clinical trial, obese individuals (BMI = 39.6 kg/m^2; 25% with IGT or IFG) were randomized to receive exenatide or placebo with lifestyle intervention for 24 weeks. A 5.1 kg body weight decrease from baseline was obtained in exenatide-treated individuals versus 1.6 kg with placebo and 77% reverted to NGT [122]. In a double-blind, placebo-controlled, 20-week trial (n = 371; age = 45.9 y, BMI = 34.9 kg/m^2), liraglutide decreased conversion of IGT to T2DM by 84 – 96% [124]. Sixty-one percent of subjects lost > 5% body weight, and 19% lost > 10% body weight. Incidence of metabolic syndrome was reduced by 60%, and systolic/diastolic blood pressure declined by 5.7/3.7 mm Hg. In the 2-year follow-up of the study, weight loss was maintained; IGT prevalence was reduced by 54 and 52 – 62% of liraglutide-treated individuals with prediabetes at randomization reverted to NGT [125].

4.3.2.3 *DDP-4 inhibitors*

DDP-4, the enzyme that cleaves GLP-1 (and GIP), increases plasma GLP-1 levels but, because the increase in plasma GLP-1 level is highly dependent upon endogenous GLP-1 (and GIP) secretion, the magnitude of increase in plasma GLP-1 (and GIP) is quite modest compared to that achieved with GLP-1 receptor agonists [126]. Thus, the increase in insulin and inhibition of glucagon secretion are quite modest [117].

Some data in animal models suggest that endogenous GLP-1 might influence progression of prediabetes to T2DM. In insulin-resistant Zucker obese rats, DPP-4 inhibitor normalized glucose excursion after oral glucose administration and delayed development of hyperglycemia [127]. Similarly, in pre-diabetic db/db mice, the increase in intact GLP-1 levels was associated with β-cell preservation and delayed progression to diabetes following treatment with alogliptin [128].

Few studies examining the effect of DPP-4 inhibitors in prediabetic individuals have been carried out in human, and the results are unimpressive. IGT subjects treated with vildagliptin for 12 weeks manifested a small increase in β-cell function, which was completely lost upon drug wash out [129]. Sitagliptin treatment for 8 weeks caused a modest improvement in β-cell function (disposition index) in IFG subjects, but this was not sufficient to alter endogenous glucose production or insulin-stimulated glucose uptake [130]. This lack of effect was confirmed in another study, which showed that 4 weeks of sitagliptin administration increased plasma incretin levels and decreased FPG in IFG subjects without changing whole body or hepatic insulin sensitivity or indices of β-cell function [131]. In summary, DPP-4 inhibition might have the potential to improve glucose homeostasis in people with prediabetes, but long-term studies are needed to explore whether augmenting endogenous incretin hormones can delay or reverse the loss of functional β-cell mass that underlies the development and progression of T2DM. To our knowledge, no outcome studies have examined the effect of DPP-4 inhibitors on the conversion rate of IGT to T2DM. Because the effect of DPP-4 inhibitors on β-cell function is modest and they do not promote weight loss, GLP-1 receptor agonists are more likely to be effective in preventing progression of prediabetes to T2DM.

4.4 α-Glucosidase inhibitors

Both acarbose in STOP-NIDDM [132] and voglibose in a Japanese trial [133] were reported to modestly (~ 25%) decrease IGT conversion rate to T2DM. Although this

preventive effect was felt to result from inhibition of carbohydrate absorption, α-glucosidase inhibitors augment incretin secretion [134], and this could explain, in part, their beneficial effects on glucose homeostasis. By altering gut microbiota flora, α-glucosidase inhibitors could also exert a beneficial effect on glucose tolerance [135].

4.5 Insulin

In the ORIGIN trial, basal insulin glargine caused a modest reduction in the incidence of diabetes in prediabetic individuals but this was accompanied by significant weight gain and hypoglycemia [136]. Moreover, a key tenet of diabetes prevention is to delay/prevent the development of β-cell failure and the need for insulin. It makes little sense to provide exogenous insulin to prevent progressive β-cell failure and, thus, the need for insulin.

5. Risk/benefit of pharmacologic therapy for prediabetes

All medications are associated with side effects, and these must be weighted agonist the benefit of progression to overt diabetes and the associated long-term complications of chronic hyperglycemia. Between 10 and 20% of metformin-treated patients experience gastrointestinal side effects (nausea, vomiting, diarrhea) and cannot tolerate the drug. Although lactic acidosis is a potential complication of metformin therapy, this is a very rare side effect and would not be expected in prediabetic individuals who have normal renal function. Weight gain, fluid retention and bone fractures are dose-related complications of pioglitazone therapy [109] and can be minimized/avoided completely by not exceeding a daily dose of 30 mg/day when combined with low doses of metformin as demonstrated in the CANOE study [116]. Of particular note, the greater the weight gain, the greater is the decrease in HbA1c [114], and fluid retention can be prevented by distally acting diuretics [137]. Bone fractures largely are observed in postmenopausal women [138] and can be avoided by not using the drug in this group. The 10-year FDA-mandated study for bladder cancer is now in its 8th year and the hazard ratio for bladder cancer is 0.98 (raw data) and 1.06 after accounting for known risk factors for bladder cancer [139]. The 8-year follow-up of the PROactive Study also shows no increased incidence of bladder cancer or any other cancer [140]. The major side effect of the GLP-1 receptor agonists is nausea, which usually is mild and transient, subsiding within 2 – 3 weeks. Postmarketing cases of pancreatitis have been associated with the GLP-1 receptor agonists, as well as with the DPP4 inhibitors, but a causal association is lacking [141-143]. From the pragmatic standpoint, it is difficult to get patients, especially those with 'prediabetes', to take an injection. The DPP4 inhibitors are largely devoid of side effects, but their effect to augment insulin secretion and preserve β-cell function is weak. The α-glucosidase inhibitors are associated with gastrointestinal discomfort and flatulence, and this has limited their use in the US.

In summary, we feel that combination therapy with low-dose pioglitazone (15 – 30 mg) with low-dose metformin (1 – 1.5 g/day) represents the most efficacious therapy with the most favorable side effect profile. Although the GLP-1 receptor agonists have a very favorable benefit/risk profile, the injection barrier with the currently available GLP-1 analogs represents a major obstacle to compliance.

6. Conclusions

Type 2 diabetes is a major global health problem, and its prevalence is rapidly increasing. Early detection and prevention of the disease would have enormous individual, social and financial benefits. Individuals with IGT and IFG are insulin resistant (in muscle and liver, respectively) and manifest a major impairment in β-cell function. From the pathophysiologic standpoint, these individuals can be considered to have T2DM. Thus, pharmacologic therapy at the prediabetes stage represents a logical time to intervene to prevent development of hyperglycemia and reverts glucose tolerance back to normal. Although behavioral modification (diet/exercise) is effective in preventing conversion of IGT and/or IFG to T2DM, in most individuals, weight loss is difficult to maintain on a long-term basis. Pharmacological interventions (combined with diet/exercise) that improve and preserve β-cell function and enhance insulin sensitivity represent logical choices for treatment of high-risk individuals with IGT (**Table 1**). TZDs and metformin prevent development of T2DM in subjects with IGT and/or IFG, but TZDs are twice as effective as metformin. Since TZDs and metformin work via different mechanisms, combination therapy with low doses of both drugs, as in the CANOE study, may represent the optimal approach. GLP-1 analogs also exert many beneficial metabolic effects that make them ideal agents for treating IGT; they augment β-cell function, promote weight loss, improve cardiovascular risk factors, do not cause hypoglycemia and are given once daily (liraglutide) or once weekly (Bydureon™). Finally, combination therapy with a TZD, metformin and GLP-1 receptor agonists represents the most rational therapeutic approach, based upon pathophysiology, in prediabetic individuals. The preceding approach is based on: i) the pathophysiology of IGT and IFG and ii) the expected response to therapy based on published results in the literature. It does not take into account the medication cost, which can be substantial, especially with the newer medications, or the long-term financial savings and improved quality of life associated with prevention of/delay in onset of diabetic microvascular complications.

7. Expert opinion

Whether early pharmacologic intervention with agents that correct known pathophysiologic disturbances present in

prediabetic individuals prevents or simply delays the onset of overt T2DM remains to be determined. This is a major health care concern because long-term lifestyle alterations in Westernized countries are difficult to implement and maintain. Although it is reasonable to assume that prevention of hyperglycemia will prevent the microvascular complications, it is less certain that the maintenance of normoglycemia will prevent the macrovascular complications. Hyperglycemia is a weak risk factor for cardiovascular disease and attempts to improve glycemic control in T2DM patients have been largely unsuccessful. Whether institution of pharmacologic therapy at the stage of IGT/IFG will prevent/reduce macrovascular complications remains to be determined. Type 2 diabetes is an inherited disorder that is aggravated by weight gain and lack of physical exercise. Because these lifestyle changes are acquired, it is reasonable to assume that metabolic abnormalities will be reversible if intervention is instituted early in the natural history of T2DM, that is, at the stage of IGT or IFG. At present, the genes responsible for insulin resistance and progressive β-cell failure in T2DM have yet to be identified, making pharmacogenetics a promising, albeit premature, approach for identifying and treating individuals with prediabetes. Until the genetic basis of T2DM is established and specific therapies are developed to reverse the basic molecular etiology of the disease, it is unreasonable to think that the natural history of T2DM can be altered on a permanent basis, that is, the disease can be prevented after medical therapy (although initially successfully) is withdrawn. Consistent with this, STOP-NDDIM and DPP studies demonstrated that, after drug discontinuation, diabetes incidence was more than doubled compared to the control group, indicating that the beneficial effect of the drug was lost upon discontinuation. Thus, in both trials, the drugs acted by 'treating' IFG and IGT subjects but did not change the natural history of the disease. In contrast, in DREAM (rosiglitazone) and ACT NOW (pioglitazone), TZD therapy, by improving insulin resistance and β-cell dysfunction, was associated with a decreased conversion rate of IGT to T2DM after discontinuation of the drug. However, within 1 year, the conversion rate to diabetes returned to that observed in placebo-treated subjects. Although this represents an alteration of the natural history of the diseases, T2DM clearly was not prevented.

At the present time, what is the 'best' pharmacologic intervention to slow the progression of IGT/IFG to T2DM? The DPP Research Group [144,145] concluded that: "Over 3 years, metformin was clinically effective (in preventing diabetes in IGT subjects) and cost-effective from the perspective of a health system and society, especially if implemented with generic medication pricing". A similar conclusion has been reached using model-simulated data [146,147]. No data on the cost-effectiveness of pioglitazone or GLP-1 receptor agonists are available. Because pioglitazone [16] is more than twice as effective as metformin [67] in reducing IGT conversion to T2DM, it is reasonable to extrapolate that pioglitazone, like metformin, also would be cost-effective. However, the costs of monitoring and treating the side effects of these drugs also need to be considered. These include the management of gastrointestinal side effects which frequently occur with metformin (10 – 20% of individuals), edema which occurs in 5 – 10% of individuals treated with TZDs, and the potential need to monitor fractures in postmenopausal women receiving TZDs. Although some observational studies have suggested an increased risk of bladder cancer in subjects who received 45 mg of pioglitazone for > 2 years, 8-year follow-up analysis of the Kaiser Permanente data (mandated by FDA) reported a hazard risk ratio of 0.98 for diabetic subjects who received pioglitazone compared to those who never used pioglitazone [139].

Because of the high price of GLP-1 analogs, which are not expected to be generically available for several years, their cost-effectiveness for treatment of prediabetes would need to be carefully examined. From the standpoint of the individual (as opposed to the societal perspective), any intervention that prevents/delays onset of hyperglycemia would be expected to prevent/reduce incidence of microvascular complications (retinopathy, nephropathy, neuropathy). At the present time, it is not possible to estimate cost benefit for preventing/reducing incidence of blindness, end-stage renal disease and amputation with GLP-1 receptor agonists.

It could be argued that institution of aggressive pharmacologic therapy at the time of diagnosis of T2DM would be as effective in prevent complications and restoring normoglycemia as intervening at the stage of IGT or IFG. With regard to this approach, institution of aggressive blood glucose control at the time of diagnosis of diabetes in UKPDS decreased, but did not prevent, development of microvascular complications [4]. Moreover, the time of onset of diabetes, as defined by the PG level (FPG or 2-h PG) or the HbA1c, is somewhat arbitrary, because conversion from 'euglycemica' to dysglycemia is a continuous and insidious process. Further, 10 – 15% of 'prediabetic' individuals already have evidence of diabetic microvascular complications. Also, many studies [148,149] have demonstrated a significant reduction in β-cell mass at the prediabetic stage with a further decline with progression to overt T2DM. At present, no therapies have been shown to increase β-cell mass in humans and individuals in the upper tertile of IGT already have lost 70 – 80% of their β-cell function and have a significant reduction (30 – 40%) in β-cell volume. Since prediabetic individuals already manifest all of the pathophysiological abnormalities present in overt T2DM and a significant minority (~ 10 – 15%) manifest diabetic microvascular complications, it seems reasonable to institute pharmacological (plus lifestyle) therapy at the prediabetic stage, especially in high-risk individuals, rather than wait for the diagnosis of diabetes, which is somewhat arbitrary and based on the PG level and not on pathophysiology, loss of β-cell mass, or presence of microvascular complications. Lastly, physician inertia in instituting and advancing therapy is a major obstacle in achieving optimal glycemic control. No study has compared or is likely to compare therapy instituted at the prediabetic stage versus at the diabetic stage, because it will require

a large sample size and a very long observation period to demonstrate a difference in the incidence of diabetic microvascular complications. Thus, a definitive answer as to when to institute pharmacological therapy, that is, in high-risk prediabetic subjects or in diabetic subjects at time of diagnosis, is unlikely to be forthcoming. In our opinion, initiation of pharmacologic therapy with diet/exercise in high-risk IGT individuals represents the best approach to prevent type 2 diabetes and its associated microvascular complications.

Declaration of interest

RA DeFronzo is on the advisory boards of Amylin, Takeda, Bristol-Myers Squibb, AstraZeneca, Novo Nordisk, Janssen, Lexicon and Boehringer Ingelheim. He has received research support from Amylin, Bristol-Myers Squibb, Boehringer Ingelheim and Takeda; and is on the speaker's bureau of Novo Nordisk, Bristol-Myers Squibb, AstraZeneca and Janssen. The other authors declare no conflicts of interest.

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