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Diabetes prevention: Can insulin secretagogues do the job?

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Abstract

The recent Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial reported that nateglinide, a non-sulfonylurea insulin secretagogue, failed to prevent progression from impaired glucose tolerance to diabetes. In order to determine the beneficial effect of insulin secretagogues as a class in diabetes prevention, we performed a literature search for randomized controlled studies and review articles on diabetes prevention and use of sulfonylureas, nateglinide, and meglitinide in PubMed and Ovid Medline since 1950. Three studies were identified with none of them reporting success in preventing diabetes, indicating that insulin secretagogues should not be recommended for diabetes prevention.

Keywords

Diabetes; Diabetes prevention; Lifestyle intervention; Insulin secretagogues; Insulin sensitizers

1. Introduction

The prevalence of diabetes around the world is alarmingly high and it is only growing. The World Health Organization (WHO) estimated that in 2000 there were 171 million people with diabetes in the world and by 2030, that number is expected to rise to 366 million [1]. The American Diabetes Association (ADA) estimated that in 2007 there were 23.6 million people in the US suffering from diabetes, which made up 7.8% of the population [2]. Diabetes also has an effect on the mortality in the United States; it was the 7th leading cause of death in 2007 [3]. A recent report calculated that the annual spending on diabetes in the US is expected to climb from \$113 billion in 2009 to \$336 billion by 2034 [4].

More startling, though, is the number of people in the US who are at risk of developing type 2 diabetes mellitus. The ADA estimates that there are 57 million people in the US with pre-diabetes, which is characterized by impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) [2]. The annual incidence of diabetes in individuals with IFG, IGT, and IFG/IGT range from 1.6 to 34%, 1.8 to 16.8%, and 10 to 15%, respectively [5]. Although it may take years, it is estimated that up to 70% of the pre-diabetic population will go on to develop type 2 diabetes [6]. This data underscores the need to find cost-effective forms of diabetes prevention.

2. Pathophysiology

Type 2 diabetes mellitus (T2DM) encompasses a group of heterogeneous disorders characterized by a defect in insulin secretion and increased cellular resistance to the action of insulin resulting in hyperglycemia and other metabolic disturbances [7]. T2DM is a progressive disease, preceded with a period of insulin resistance and IGT. Endogenous insulin secretion is increased by the β -cells in early stages in order to maintain fasting blood glucose within the normal range. However, the progressive nature of T2DM's insulin secretory defect leads to increased postprandial blood glucose (IGT) followed by fasting hyperglycemia and frank diabetes. Studies in Pima Indians and white British civil servants in the Whitehall II study reported that peripheral insulin resistance is required for β -cell failure to occur in susceptible individuals [8,9]. Studies on insulin secretion and action in pre-diabetes have shown that in IFG the first-phase insulin secretion is lost and insulin resistance is primarily at the level of the liver, resulting in exaggerated endogenous glucose production [10,11]. Patients with IGT have diminished first- and second-phase insulin secretion and profound insulin resistance in peripheral tissues, primarily in skeletal muscle [11]. The conversion from IGT to T2DM may take from 9 to 12 years unless there are lifestyle modifications or other therapies instituted to reduce this risk. Environmental factors such as level of physical activity and adiposity [12], increased free fatty acids [13,14], and genetic factors, such as variants in KCNQ1 (ATP-dependent potassium channel) gene [15], MTNR1B (melatonin receptor 1B) [16], and transcription factor-7-like 2 (TCF7L2, a transcription factor in Wnt signaling) [17], have been shown to modulate β -cell function, insulin sensitivity, and progression to T2DM.

Several randomized controlled studies have shown that lifestyle modifications and oral antidiabetic treatment with metformin, thiazolidinediones, and acarbose can effectively prevent diabetes development in high risk populations. The most recent study to attempt prevention of diabetes with a pharmacologic agent, the NAVIGATOR trial, reported that nateglinide, a non-sulfonylurea insulin secretagogue, failed to prevent progression from impaired glucose tolerance to T2DM [18]. The results of this study prompted us to investigate the results of previous trials using insulin secretagogues for the prevention of T2DM, to determine if there was additional evidence that a drug's mechanism of reducing hyperglycemia is important toward preventing diabetes. We performed a search of the biomedical journal literature from PubMed and Ovid Medline from 1950 to June 2010. We analyzed the results of English-language, randomized controlled studies, and review articles found under the subject headings diabetes prevention, insulin secretagogues, sulfonylureas, nateglinide, meglitinide, and oral antidiabetic agents.

3. NAVIGATOR study

The recently reported randomized controlled trial in diabetes prevention, the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, demonstrated no beneficial effect of nateglinide in stopping the progression from pre-diabetes to diabetes compared to placebo [18]. The NAVIGATOR Study Group randomized 9306 adult subjects with IGT and cardiovascular disease or cardiovascular risk factors to receive placebo or nateglinide (60 mg before meals, three times daily), along with a study-specific lifestyle modification program [18]. Researchers chose to use nateglinide because they hypothesized that it might reduce the risk of progression to diabetes by restoring a more physiologic insulin response to meals [18]. Additionally, it was felt that reducing postprandial hyperglycemia could have a protective effect on the risk of cardiovascular events [19]. The lifestyle modification program was recommended to all patients and was designed to achieve and maintain a 5% weight loss, reduce the amount of saturated and total fats in their diets, and increase their physical activity. The study reported that 36.0% of

participants in the nateglinide group developed diabetes while 33.9% in the placebo group progressed to diabetes after a median follow-up of 5.0 years (hazard ratio 1.07 [95% CI 1.00–1.15], $p = 0.05$). Compared with placebo, nateglinide lowered fasting plasma glucose by 0.03 mmol/L, but increased 2-h postprandial glucose by 0.24 mmol/L. In addition, 10% of all participants lost 5% of their baseline weight by 6 months, however, the nateglinide group had an overall higher mean body weight throughout the entire study (mean difference 0.35 kg, $p < 0.001$).

Nateglinide is a non-sulfonylurea insulin secretagogue with a unique chemical structure different from other hypoglycemic agents [20]. It is this structure that allows it to have fast association/dissociation kinetics at the β -cell than other drugs in its class, helping to mimic the physiological early-phase insulin secretion. In rodent models of T2DM, nateglinide improved early-phase insulin secretion and glucose tolerance without increasing overall insulin secretion compared with controls. It has been thought that these properties would allow it to reduce postprandial glucose levels effectively in patients with and, potentially, pre-diabetes. Studies have shown that in patients with known diabetes, nateglinide may have a modest effect on hemoglobin A1c reduction with a mean reduction of 0.54% after 24 weeks of treatment [21]. The goal in diabetes prevention with this strategy was to return insulin secretion toward normal physiologic patterns and the body to normoglycemia, regardless of insulin resistance and amount of insulin needed. However, the NAVIGATOR failed to demonstrate these expectations in the large randomized study.

4. Trials using other insulin secretagogues for the prevention of diabetes

In addition to the recently reported NAVIGATOR study, two previous studies investigated the effect of sulfonylureas in the prevention of diabetes (Table 1) and six additional trials studied the effects of insulin secretagogues on fasting and post-prandial glucose homeostasis in patients with pre-diabetes.

The Bedford trial [22] in 1962 randomized 248 male and female “borderline diabetics” to either treatment with a sulfonylurea, tolbutamide, or placebo. The main goal of the trial was to reduce the manifestations of arterial disease, with a secondary outcome looking at diabetes prevention and glycemic control. Patients were divided between treatment arms and then each group was further randomized to a carbohydrate restricted diet or no dietary intervention. The dose of tolbutamide was 500 mg twice daily. The 8.5-year cumulative incidence of diabetes was 9% in the tolbutamide group and 8% in the placebo group (incidence rate ratio 1.1, 95% CI 0.5–2.5) and a subsequent report after the 10-year follow-up of these patients also showed no significant effect of tolbutamide on the incidence of diabetes. Both groups assigned to carbohydrate restriction lost a greater proportion of body weight than the groups without dietary intervention [23]. At 10 years, body mass index (BMI) was significantly greater in those patients that progressed to diabetes; however, allocation to treatment group or dietary intervention were not significantly associated with higher incidence of diabetes or postprandial glucose levels [22]. The authors concluded that there is no advantage of tolbutamide treatment over placebo in preventing diabetes when dietary modifications are implemented.

The Malmohus study [24] assessed the effects of tolbutamide and dietary intervention in subjects with IGT from a large diabetes detection survey over a 10-year follow-up period in Sweden. Participants, all men, were randomized into four groups: tolbutamide and diet intervention, placebo and diet, diet alone, or no intervention. A fifth group of men with normal glucose tolerance was later added as a control group and was compiled retrospectively from the original detection survey. In the dietary intervention groups, subjects were instructed on how to limit their total intake of carbohydrates and fat, as well as

total energy intake if subjects were found to be overweight. All groups underwent annual oral glucose tolerance tests (OGTT) to detect the development of diabetes. The dose of tolbutamide was 500 mg three times daily. The 10-year cumulative incidence of diabetes was 10% in men assigned tolbutamide treatment and 13% in the group assigned placebo or no drug (incidence rate ratio 0.8, 95% CI 0.3–2.0). A total of 49 subjects were randomized to receive tolbutamide; of them, 26 stopped the medication prematurely and two additional patients were found to have non-measurable serum tolbutamide levels despite claiming to have taken the medication. Among the 23 subjects who completed the 10-year intervention, tolbutamide treatment prevented all new diabetes cases compared to 17 out of 59 subjects (29%) in the untreated group. However, taking into account the greater than 50% drop-out rate in the treatment group, an intention-to-treat analysis suggested minimal or no effect of tolbutamide on diabetes prevention [25]. The authors also reported that glucose tolerance improved, more in the intervention groups, but no data or definition of normal glucose tolerance was given.

Six trials also assessed the effects of insulin secretagogues on β -cell function and glycemic control in pre-diabetic subjects with IGF and IGT. These studies were of short duration, ranging from 6 months to 2 years, and were not primarily aimed at the prevention of diabetes. Papoz et al. [26] analyzed the effects of glibenclamide treatment over 2 years in male subjects and reported no difference compared to placebo on postprandial or fasting glucose levels. Ratzmann et al. [27] reported no effects of glibenclamide plus diet on glucose tolerance and insulin secretion over two years of treatment in non-obese subjects. Two other studies with the use of the 2nd generation sulfonylurea, gliclazide, reported significant reductions in fasting plasma glucose by 0.5–0.7 mmol/L compared to placebo treatment [28,29]. Karunakaran et al. [29] reported a reduction in fasting but an increase in postprandial glucose levels after gliclazide administration for 12 months. More recently, Osei et al. [30] studied the effects of glipizide treatment over 2 years in combination with lifestyle modification in African-Americans, and reported a significant reduction in both postprandial and fasting glucose compared to placebo. We have found several studies that demonstrated inconsistent effects of nateglinide on glycemic values. One study showed a reduction in postprandial glucose without a significant effect on fasting glucose levels [31]. Yet, the recent NAVIGATOR study reported an increase in postprandial glucose levels and a decrease in fasting glucose concentration which is likely explained by the longer duration of the NAVIGATOR study [18].

5. Trials using non-insulin secretagogues for the prevention of diabetes

Several randomized, controlled studies have assessed the efficacy of oral hypoglycemic (thiazolidinediones, metformin and acarbose) and weight loss (orlistat) agents in the prevention of T2DM (Table 1).

5.1. Metformin

The mechanism of action of metformin is not completely understood, but in the presence of insulin it functions to reduce the liver's production of glucose, increasing the body's sensitivity to insulin [32]. The Diabetes Prevention Program (DPP) was a major multicenter clinical research study aimed at discovering whether modest weight loss through dietary changes and increased physical activity (lifestyle intervention) or treatment with the oral diabetes drug metformin (850 mg twice a day) versus placebo could prevent or delay the onset of T2DM in patients with IGT [33]. Participants in the lifestyle intervention group had a reduced incidence of diabetes by 58% compared to placebo. Lifestyle changes worked particularly well for participants aged 60 and older, reducing their risk by 71%. Participants taking metformin had a reduced incidence of diabetes by 31% compared to placebo. Metformin was effective for both men and women, but it was least effective in people aged

45 and older. People 25–44 years old and in those with a body mass index of 35 or higher benefited the most from metformin. In addition, at 1 year, the study investigators showed preservation of β -cell function with metformin compared with placebo [34]. Similarly, the Indian Diabetes Prevention Programme (IDPP) evaluated 531 native Asian Indian patients with IGT randomized to one of four groups: control, lifestyle modification, metformin (250 mg twice daily), or metformin plus lifestyle modification [35]. Compared to placebo, metformin significantly reduced the incidence of diabetes after a median of 30 months of therapy (relative risk reduction (RRR): 26.4%, $p = 0.029$).

5.2. Thiazolidinediones

Thiazolidinediones (TZDs) are peroxisome-proliferator-activated receptor γ (PPAR γ) agonists, which are nuclear receptors that when activated cause the transcription of genes that affect carbohydrate and lipid metabolism [32]. Although the complete mechanism is not understood, they are known to improve insulin sensitivity. Three studies have reported that TZD therapy is highly effective in preventing T2DM. The Troglitazone Intervention for the Prevention of Diabetes trial (TRIPOD) evaluated the benefit of troglitazone in 266 Latino women with a history of gestational diabetes [36]. Patients were randomized shortly after pregnancy to troglitazone or placebo and treatment was for a median of 2.5 years. The study reported a 59% decrease in the incidence of diabetes compared with placebo (cumulative incidence of diabetes 5.4% vs. 12.1%; HR 0.44 [95% CI 0.25–0.83]) [36]. In addition to a decrease in diabetes incidence, troglitazone was found to significantly decrease fasting plasma glucose (94.5–91.0 mg/dL, $p = 0.0001$). The troglitazone also showed an increase in insulin sensitivity while decreasing insulin secretion compared to no change in either by placebo (sensitivity (S_I): $2.60\text{--}3.76 \text{ min}^{-1}/\mu\text{U/mL} \times 10^{-4}$, $p < 0.0001$; secretion (insulin area): $9402\text{--}6551 \mu\text{U/mL} \times \text{min}$, $p < 0.0001$).

The Diabetes Prevention Program (DPP), which compared lifestyle intervention and metformin to placebo, also included a troglitazone arm that was discontinued early because of removal of the product from the market [37]. At the time of discontinuation, troglitazone produced the most significant reduction in the progression to diabetes compared to lifestyle intervention and placebo therapy over its 0.9 year usage, decreasing the incidence of diabetes by 75% compared to placebo ($p < 0.001$).

Similarly, the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial showed a 60% reduction of progression to diabetes in IFG and IGT patients using rosiglitazone compared to placebo (HR 0.40 [95% CI 0.35–0.46]) [38]. In addition, 50.5% of individuals in the rosiglitazone group versus 30.3% in the placebo group became normoglycemic during the trial ($p < 0.0001$).

More recently, the Canadian Normoglycemia Outcomes Evaluation (CANOE) trial showed that a combination of low-dose rosiglitazone and metformin can reduce the incidence of diabetes by 66% (13.6% vs. 39.4% placebo, $p < 0.0001$) [39]. There was also no change in insulin sensitivity in the treatment group, while the placebo group had a worsening in sensitivity (IS_{OGTT} : -0.39 vs. -1.24 , $p = 0.0006$). Additionally, 79.6% of the rosiglitazone/metformin group versus 53.1% of placebo returned to normal glucose tolerance ($p = 0.0002$). β -Cell function did not change in either group. The examination of the studies in which TZDs were used for the prevention of diabetes demonstrates that in addition to improved insulin sensitivity they prevent deterioration of β -cell function [37,40].

5.3. Acarbose

Acarbose is a weak hypoglycemic agent that inhibits the alpha-glucosidase enzyme in the brush border of the small intestines [32]. Inhibition of this enzyme reduces the rate of

digestion of complex carbohydrates, thereby reducing the amount of glucose produced and absorbed from food. The use of acarbose in the Study to Prevent Non-insulin Dependent Diabetes Mellitus (STOP-NIDDM) prevention trial resulted in a 25% decrease in the progression to diabetes among overweight and obese patients with IGT compared to placebo [41]. Diabetes developed in 32% of patients taking acarbose and 42% of those taking placebo, reducing the likelihood of developing diabetes by 25% (relative hazard ratio: 0.75 [95% CI 0.63–0.90], $p = 0.0015$). Reversion to normal glucose tolerance was seen in 35% of patients taking acarbose versus only 31% on placebo ($p < 0.0001$).

5.4. Orlistat

Orlistat is a gastrointestinal tract lipase inhibitor which decreases intestinal fat absorption leading to modest but sustained weight loss [42]. The XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study evaluated the benefit of lifestyle modification with orlistat or placebo in obese patients with normal glucose tolerance (NGT) or IGT [43]. Orlistat patients had a 37.3% decrease in the risk of developing diabetes ($p = 0.0032$) and a significantly greater amount of weight loss than placebo (5.8 vs. 3.0 kg, $p < 0.001$). Orlistat also decreased insulin secretion significantly more than lifestyle modification alone (10.9 mmol/L vs. 8.4 mmol/L, $p < 0.01$).

6. Discussion

The natural history of type 2 diabetes mellitus (T2DM) development involves conversion from normal glucose tolerance to IGT or IFG with 50–70% of such individuals subsequently progressing to T2DM over the next decade [6,13]. Although reduced insulin secretion and insulin sensitivity are present at the onset of T2DM [10]; impaired insulin sensitivity is present before β -cell dysfunction in most patients with pre-diabetes [7–10], suggesting that the alleviation of insulin resistance appears to be the most successful target for diabetes prevention. Multiple randomized trials on diabetes prevention have been diverse and include lifestyle and pharmacologic interventions. The results of these trials show lifestyle interventions seem to be at least as effective as pharmacologic interventions [44]. The increase in obesity and decrease in physical activity in Westernized societies are strongly linked with the increase in the prevalence and incidence of T2DM. Lifestyle interventions, which aim to reduce obesity and increase physical activity, help to directly address these risk factors.

Lifestyle modification may be considered an ideal method of diabetes prevention because of beneficial effects on the entire cardiovascular risk profile as well as non-cardiovascular benefits related to weight loss and an improved diet [45,46]. However, long-term adherence to such interventions, their feasibility in a non-trial setting, and unknown effects on cardiovascular outcomes remain potentially limiting factors to widespread implementation [47].

Pharmacological therapy to prevent T2DM may be an important therapeutic modality in those patients in whom lifestyle interventions fail, are not sufficiently potent, or are not feasible [48]. A number of randomized control trials have examined the impact of different oral antidiabetic and weight loss drugs on diabetes incidence. Drugs that improve insulin sensitivity have been shown to successfully reduce the progression from pre-diabetes to T2DM (DPP, TRIPOD, IDPP, DREAM) [33,35,36,38]. The adequately powered studies have shown significant decreases in diabetes incidence with biguanides (metformin), glitazones (pioglitazone, rosiglitazone), and alpha-glucosidase inhibitors (AGIs; acarbose, voglibose), reducing the relative risk of diabetes by 40%, 64%, and 27% respectively, compared with control. Some of these trials also reported prevention in the reduction of β -cell function [34,37,40]. Based on these findings one can speculate that improving insulin

sensitivity can preserve β -cell function by reducing the physiological demand for basal and/or prandial insulin secretion via increased peripheral insulin sensitization. Several studies have evaluated the impact of insulin secretagogues on β -cell function and in the progression from pre-diabetes (IFG and IGT) to diabetes. The use of insulin secretagogues results in an initial improvement in glycemia [28–30], but the long-term protective effects on β -cell function and diabetes prevention are elusive. Indeed, no reduction in diabetes incidence has been reported with the first-generation sulfonylurea tolbutamide, or with the second generation sulfonylurea gliclazide in the prevention of diabetes [18,22,24,29]. In agreement with these reports, the results of the NAVIGATOR trial show that among persons with IGT and cardiovascular disease or cardiovascular risk factors, assignment to nateglinide, at a dose of 60 mg three times daily, as compared with placebo, in addition to a lifestyle modification program, did not reduce the incidence of diabetes or cardiovascular outcomes. Thus, all trials (Table 1) that used secretagogues for diabetes prevention in pre-diabetic individuals convincingly demonstrated that this class of medications did not prove to be a part of current diabetes preventive strategies.

An exciting arena for future diabetes prevention trials could include enrollment of individuals with heightened susceptibility for T2DM based on genetic studies. Recent analyses of diabetes-associated variants in non-diabetic populations has revealed that most of the genes so far examined have an association with insulin secretion (including *KCNJ11*, *TCF7L2*, *HNF1*) [49], while only two genes *FTO* (fat mass- and obesity-associated) and *PPAR γ 2* are shown to affect insulin sensitivity [50,51]. Polymorphisms in *KCNJ11* and *ABCC8*, as well as the common Pro12Ala polymorphism of *PPARG* were shown to influence the risk of developing diabetes in the prospective Botnia study [52]. Polymorphisms of the *SUR1 (ABCC8)* and *Kir6.2 (KCNJ11)* genes predict the conversion from IGT to T2DM in the Finnish Diabetes Prevention Study [53]. In another study, the type 2 diabetes-associated *PPARG* P12A polymorphism was found to have little or no effect on the favorable response to troglitazone [54]. The roles of these genetic polymorphisms need to be confirmed in prospective studies. Knowing the critical role of β -cell failure in the pathogenesis of type 2 diabetes mellitus and that over half of the patients with pre-diabetes develop the disease, it would be of utmost interest to examine specific pharmacologic and lifestyle change strategies in the selected groups of subjects.

Current ADA guidelines emphasize the use of lifestyle modification to prevent or delay T2DM. Metformin is the only pharmacologic treatment recommended for diabetes prevention and only for those with pre-diabetes (combination of IGT and IFG) and an additional risk factor such as glycated hemoglobin >6%, hypertension, dyslipidemia, or a first-degree relative with diabetes [46].

In summary, much progress has been made over the past decades in the identification of effective strategies to prevent or delay onset of T2DM. Oral antidiabetic drugs that target insulin sensitivity, such as metformin and thiazolidinediones, as well as agents that unload the β -cell by lowering carbohydrate absorption from the gastrointestinal tract or by inducing weight loss have been shown to be successful in preventing the progression from IGT and IFG to diabetes. In contrast, all clinical trials that have used insulin secretagogues, including the NAVIGATOR trial, have failed to reduce the progression from pre-diabetes to diabetes. These results indicate that insulin secretagogues cannot be recommended for the prevention of diabetes in high-risk individuals and that future research should move away from such trials.

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Table 1

Randomized controlled trials examining the effects of different pharmacologic agents on the progression to diabetes.

Study	Population	Intervention vs. placebo	Effect of intervention on progression to diabetes
Sartor et al. [24] Malmohus study	IGT <i>N</i> = 186	Tolbutamide and diet	Progression to diabetes: tolbutamide 10%, placebo 13%. HR: 0.8, 95% CI 0.3–2.0
Keen et al. [22] Bedford trial	IGT <i>N</i> = 248	Tolbutamide and diet	Progression to diabetes: tolbutamide 9%, placebo 8%. HR: 1.1, 95% CI 0.5–2.5
NAVIGATOR [18]	IGT <i>N</i> = 9306	Nateglinide and LSM	Progression to diabetes: nateglinide 36.0%, placebo 33.9%. HR: 1.07, 95% CI 1.00–1.15
DPP [33]	IGT, IFG <i>N</i> = 3234	Metformin LSM	Progression to diabetes: metformin 21.7%, LSM 14.4%, placebo 28.9%. HR: metformin 0.69, 95% CI 0.57–0.83 LSM 0.42, 95% CI 0.37–0.52
CANOE [39]	IGT <i>N</i> = 207	Rosiglitazone and metformin	Progression to diabetes: rosiglitazone and metformin 13.6%, placebo 39.4%. HR: 0.31, 95% CI 0.17–0.58
IDPP [35]	IGT <i>N</i> = 531	LSM metformin	Progression to diabetes: LSM 39.3%, metformin 40.5%, LSM plus metformin 39.5%, placebo 55%. HR: LSM 0.623, 95% CI 0.23–1.02; metformin 0.651, 95% CI 0.27–1.04; LSM plus metformin 0.629, 95% CI 0.23–1.03
TRIPOD [36]	Women with history of GDM <i>N</i> = 266	Troglitazone	Progression to diabetes: troglitazone 5.4%, placebo 12.1%. HR: 0.44, 95% CI 0.25–0.83
DREAM [38]	IGT, IFG <i>N</i> = 5269	Rosiglitazone	Progression to diabetes: rosiglitazone 11.6%, placebo 26%. HR: 0.40, 95% CI 0.35–0.46
STOP-NIDDM [41]	IGT <i>N</i> = 1429	Acarbose	Progression to diabetes: acarbose 32%, placebo 42%. HR: 0.75, 95% CI 0.63–0.90
XENDOS [43]	Obese, normal/IGT <i>N</i> = 3305	LSM and orlistat	Progression to diabetes: Orlistat 6.2%, LSM plus placebo 9.0%. HR: 0.627, 95% CI 0.455–0.863

PPG, post-prandial glucose; FPG, fasting plasma glucose; LSM, lifestyle modification; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HR: hazard ration.