Review

Antidiabetic agents in subjects with mild dysglycaemia: prevention or early treatment of type 2 diabetes?

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Abstract

Besides lifestyle, various pharmacological treatments have proven their efficacy to reduce the incidence of type 2 diabetes in high-risk individuals, especially in those with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). Major placebo-controlled clinical trials demonstrated favourable effects of various glucose-lowering drugs generally used for the treatment of type 2 diabetes, i.e. metformin, acarbose and thiazolidinediones (glitazones). These trials showed a lower rate of progression to overt diabetes and a higher regression rate to a normal glucose status with active treatment as compared to placebo after a follow up of several years. Ongoing trials should confirm such a favourable effect with those drugs and may demonstrate a similar protective effect with other pharmacological approaches such as glinides or even basal insulin regimen. However, the reported favourable effects were generally observed while the subjects were still on treatment, and partially vanished after a rather short period of wash-out of several weeks. Therefore, the distinction between a true preventing effect and simply a masking effect is difficult with glucose-lowering drugs. In addition, as type 2 diabetes is a progressive disease, it is still questionable whether the effect corresponds to a prevention effect or only to a postponing of the development of the disease. Owing to the pathophysiology of the disease, the only way to block the progression of type 2 diabetes is probably to avoid the progressive loss of β-cell function and/or mass. Whatever, these data obtained in large clinical trials bring further argument to support early treatment of diabetes, even at a prediabetic state, in order to stop the vicious circle leading to an inevitable deterioration of glycaemia in predisposed subjects.

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Résumé

Antidiabétiques oraux chez des sujets atteints d’intoléance au glucose et/ou d’hyperglycémie modérée jeun : prévention ou traitement précoce du diabète de type 2 ?

À côté des mesures hygiénodiététiques, diverses approches pharmacologiques ont fait la preuve de leur efficacité à réduire l’incidence du diabète de type 2 chez des sujets à haut risque, en particulier ceux avec intolérance au glucose et/ou hyperglycémie modérée à jeun. Des essais cliniques importants, contrôlés versus placebo, ont démontré des effets favorables de différents médicaments antihyperglycémiants utilisés comme antidiabétiques oraux pour le traitement du diabète de type 2, comme la metformine, l’acarbose et les thiazolidinediones (glitazones). Ces études ont montré une moindre progression vers un diabète avéré et un taux plus important de régression vers un statut glycémique normal sous traitement actif par comparaison au placebo lors d’un suivi de quelques années. De nouveaux essais en cours devraient confirmer de tels effets avec ces différents médicaments et peut-être montrer des effets protecteurs similaires avec d’autres classes comme les glinides ou même avec l’administration d’une insuline basale. Cependant, ces effets favorables ont généralement été observés alors que les sujets étaient toujours sous traitement, et disparaissent partiellement dès après une période de sevrage relativement brève de quelques semaines. Dès lors, la distinction entre un véritable effet de prévention et un simple effet de « masquage » est difficile à établir avec ce type de médicaments hypoglycémiants. De plus, comme le diabète de type 2 est une maladie progressive, la question de savoir si l’effet observé correspond à une vraie prévention ou à un simple retard dans la progression de la maladie doit être posée. Au vu de la physiopathologie de la maladie, la seule façon de bloquer la progression du diabète de type 2 est probablement d’enrayer la perte progressive de la fonction et/ou de la masse des cellules β pancréatiques. Quoi qu’il en soit, les observations faites dans les grands essais cliniques apportent des arguments supplémentaires en faveur d’un traitement précoce de la maladie, y compris à un stade prédiabétique, dans le but de rompre le cercle vicieux qui conduit inéluctablement à la détérioration de la glycémie chez les sujets prédisposés.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with excess morbidity and mortality, and is considered as one of the most costly and burdensome chronic diseases of our time [1,2]. It is a dynamic disease with dual defects, i.e. a progressive insulin secretory defect combined with insulin resistance [3–5], and is intimately linked to the so-called metabolic syndrome and an increased risk of cardiovascular disease [6]. It is well established that the development of T2DM results from an interaction of a subject’s genetic makeup and environment [5]. The development of obesity seems to be an important factor promoting the development of insulin resistance [7], which in the presence of a genetically determined propensity to β-cell dysfunction results in progressive alterations in glucose tolerance (“dysglycaemia”), leading from impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) to overt T2DM [5,8,9].

Prevention programmes of T2DM depend on the identification of predisposed individuals and potentially modifiable risk factors [8–12]. Recently, a great deal of effort has been made on slowing or even preventing the development of T2DM in high-risk subjects [13,14]. In this context, a lifestyle intervention, typically comprising a combination of healthy diet and regular exercise, can reduce the risk of progression from IGT to T2DM by up to 58% [15,16]. However, lifestyle modifications cannot be implemented in all clinical settings and are not practical for all subjects [17–19]. Therefore, drug therapy targeting either insulin resistance, or beta-cell function, or both may be considered to prevent T2DM [20]. In addition to lifestyle strategies, various pharmacological approaches have already proven their efficacy in preventing or postponing T2DM in adults [21–23], and may deserve future interest in younger people [24].

The aim of the present review article is to describe and discuss the results of clinical trials demonstrating a preventive effect of various glucose-lowering agents in the development of T2DM in at risk individuals because of the presence of IFG and/or IGT. Almost all antihyperglycaemic agents used for the treatment of T2DM [25] have been assessed or are currently evaluated in clinical trials aiming to prevent the development of T2DM: insulin secretagogues (sulphonylureas and glinides), metformin, thiazolidinediones (glitazones), acarbose and even insulin (Fig. 1) [26,27]. However, because of the specific mode of action of these drugs (intrinsic glucose-lowering activity), and in contrast to what has been reported with other pharmacological classes such as inhibitors of the renin-angiotensin system [28,29], one key issue when analysing the results of these trials is to be able to distinguish between a true preventing, a postponing or only a masking effect of type 2 diabetes by the antihyperglycaemic effect of the drug [30,31].

2. Methods

We performed an extensive review of the literature on the topic. To identify relevant studies evaluating the ability to prevent type 2 diabetes with antihyperglycaemic agents, the following sources were searched: MEDLINE, EMBASE, Science citation index (Web of Science and ISI Proceedings) from January 1995 to October 2006, with the following key-words: the generic name of all available glucose-lowering compounds (metformin, acarbose, troglitazone, rosiglitazone, pioglitazone, various sulphonylureas, nateglinide, repaglinide, insulin), the metabolic characteristics of the target population (IGT, IFG, prediabetes) and the outcome of the intervention (prevention, type 2 diabetes). No language restrictions were imposed. Reference lists of original studies, narrative reviews, and previous systematic reviews were also examined.

3. Results

3.1. Metformin

Metformin is now considered as the first-line drug for the treatment of T2DM [32,33] and appears to exert several metabolic effects that may be favourable in patients with abdominal obesity and IGT [34,35]. Metformin primarily reduces glucose output from the liver, despite no reduction in liver fat [36], and could also increase, although to a rather small extent, glucose uptake in the peripheral tissues in the presence of insulin, thereby reducing demand on the β-cell. A few old studies
investigating biguanides (mainly metformin) found no significant reduction in the incidence of T2DM compared with placebo using intention-to-treat analyses. However, all of these studies had very low diabetes incidence and were likely underpowered [26].

The largest and most methodologically rigorous trial was the Diabetes Prevention Program (DPP) performed in the United States [16]. It randomised 2,155 individuals (age 51 years, BMI 34 kg/m², 45% high-risk minority groups) with IGT to metformin (850 mg b.i.d.) or placebo (another arm assessed the effect of intensive lifestyle intervention, and one arm tested troglitazone but had to be stopped prematurely; see below). After a mean follow-up period of 2.8 years, the incidence of new diabetes was 7.8% in the placebo-treated patients versus 4.8% in those treated with metformin (relative risk [RR] = 0.69, 95% confidence interval [CI] 0.57–0.83) (Table 1). To prevent one case of diabetes during a period of 3 years (number needed to treat or NNT), 14 would have to receive metformin. In post-hoc subgroup analyses, the benefits of metformin were primarily observed in young patients (< 60 years) and in obese patients (BMI > 35 kg/m²). In order to avoid a direct metabolic effect of the drug [37], subjects were submitted to a final investigation after a 1–2-week washout period. In the 79% of eligible patients who completed this last visit, the incidence of diabetes increased from 25.2% to 30.6% in the metformin group and from 33.4% to 36.7% in the placebo group [38]. Nevertheless, when results of the washout period were included in the overall analysis, metformin still significantly decreased diabetes incidence (RR = 0.75, 95% CI 0.62–0.92) (Table 2).

In the Chinese Diabetes Prevention Study (CDPS), subjects with overweight (BMI: 25 kg/m²; age: 50 years) and IGT were divided into a control group (n = 85) which received conventional education, a metformin group (n = 88; 250 mg t.i.d.) and an acarbose group (n = 88; 50 mg t.i.d.) (see below) [39]. Over a 3-year period, 34.9% in the control group versus 12.4% in the metformin group progressed to diabetes. This represents an impressive risk reduction of 76.8% for metformin, despite the absence of significant weight loss. Unfortunately, the procedure of randomisation was not described in the paper.

The Early Diabetes Intervention Trial (EDIT) was a 6-year, prospective, randomised, double-blind, placebo-controlled study in subjects thought to be at increased risk of developing diabetes, and who had two consecutive fasting plasma glucose levels in the range 5.5–7.7 mmol/l. The primary aim of this UK trial was to determine whether deterioration in glucose tolerance towards diabetes could be delayed or prevented using a biguanide (metformin, 500 t.i.d.) or an α-glucosidase inhibitor (acarbose, 50 t.i.d.) (see below) [40]. The 2 × 2 factorial design of this study has the potential to reveal a synergistic effect between metformin and acarbose on diabetes prevention. However, the double intervention group is small with just over 160 patients and may be underpowered to find such synergy. Six-year results for both arms have been published only as abstracts and primary analyses showed no significant difference between groups [40]. Of the initial cohort, 31% became diabetic and 14% discontinued follow-up. No differences were seen in RR for diabetes by 6 years with metformin (RR = 0.99; P = 0.94) or combination metformin–acarbose therapy (RR = 1.02; P = 0.91) as compared to placebo. Similarly, non-significant differences were observed versus placebo in those patients with IGT at baseline.

More recently, the Indian Diabetes Prevention Programme (IDPP-1) randomised 531 individuals with IGT in four groups,
control, lifestyle alone, metformin alone (250 mg b.i.d.) and combined lifestyle plus metformin. This trial confirmed that lifestyle modification and metformin prevent T2DM in Asian Indian subjects with IGT [41]. However, there was no added benefit from combining the two approaches after a median follow-up period of 30 months. Of note the average dose of metformin was only 250 mg twice daily, thus much lower that that used in the US DPP [16]. The 3-year cumulative incidences of diabetes were 55.0% in the control group, 39.3% in the group with lifestyle modification, 40.5% in the group treated with metformin and 39.5% in the group given lifestyle advice plus metformin. Thus, the relative reduction was 26.4% with metformin alone (95% CI 19.1–35.1, \( P = 0.029 \)), and 28.2% with combined approach lifestyle plus metformin (95% CI 20.3–37.0, \( P = 0.022 \)) (Table 1). The NNT to prevent one incident case of diabetes was 6.4 for lifestyle alone, 6.9 for metformin and 6.5 for lifestyle plus metformin. The absence of synergistic effect may be disappointing, especially because the RR reduction of diabetes with lifestyle modification was less in the Indian DPP compared with the 58% reduction in previous trials [15], especially the US DPP [16]. In this latter trial, part of the metformin effect was attributed to a modest weight loss, which was not observed with metformin in the Indian trial, possibly because of the lower daily metformin dose used.

### 3.2. Sulphonylureas/gl ginides

While defective insulin secretion has been long considered as an event in the natural history of T2DM [3], recent studies have clearly demonstrated that there is an early defect in \( \beta \)-cell function [42], even in individuals with IGT [43], especially when insulin secretion is evaluated in comparison with insulin resistance [4]. Therefore, the use of insulin secretagogue agents might be considered as a potential alternative to prevent progression to T2DM, even if the risk of hypoglycaemia may be a serious limitation in clinical practice [44]. As reviewed by Alberti [45], the first-generation compound tolbutamide showed positive results in 5 out of 7 intervention trials. However, data interpretation is complicated by the fact that these trials preceded the modern definition of IGT and studied “borderline” or “chemical” or “latent” diabetes. Two old studies examined the effect of tolbutamide therapy (1000–1500 mg/day) on diabetes incidence in patients with IGT or high-normal/elevated fasting glucose levels [46,47]. Neither study reported a statistically significant reduction in the incidence of T2DM compared with control or placebo, although both studies were small (\( n = 97 \) and \( n = 248 \)) and potentially underpowered. These negative results were confirmed in a larger and more recent trial (Fasting Hyperglycaemia Study, reported only in an abstract form) showing that gliclazide therapy over 6 years does not delay progression to diabetes [48]. In this trial, hypoglycaemia was a potentially limiting side effect of sulphonylurea therapy, occurring at a frequency of 3% in these non-diabetic patients. Perhaps an ongoing trial should provide more definitive evidence of the potential interest of sulphonylureas. Indeed, the NEPI Antidiabetes Study (NANSY) has recruited almost 2000 individuals with fasting glucose levels of 5.6–6.0 mmol/l, who will be randomised to glimepiride or placebo and followed for 5–7 years with diabetes as primary endpoint [49].

Because new insulin-secreting agents of the meglitinide family (repaglinide, nateglinide) have a more favourable pharmacokinetic profile that allows to better control postprandial hyperglycaemia while reducing the risk of late hypoglycaemia [50], they represent a possible alternative to sulphonylurea for the prevention of T2DM. No such demonstration is available yet neither with repaglinide nor nateglinide. However, a large trial (NAVIGATOR: “Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research”) is currently investigating the effect of nateglinide in high-risk subjects [51]. This multinational, randomised, double-blind, placebo-controlled, forced-titration, \( 2 \times 2 \) factorial design trial assessed the effect of nateglinide (30–60 mg t.i.d.) and valsartan (80–160 mg o.d.) on the prevention of diabetes and cardiovascular events in approximately 7500 subjects with IGT and/or IFG and increased risk for a cardiovascular event. The delay or prevention of progression to diabetes will be evaluated in the core phase of the study (3 years). The efficacy of nateglinide and valsartan will be determined prospectively using validated measures of diagnosis of diabetes, i.e. oral glucose tolerance tests (OGTTs) and/or fasting glucose levels [51].

### 3.3. Glitazones

TZDs (glitazones) are insulin-sensitisers with glucose-lowering effects, which are increasingly used for the treatment of T2DM [52]. These agents increase insulin sensitivity, both in the peripheral tissues (muscle and fat) and liver (reducing hepatic fat depot), thereby decreasing the glucose load on the \( \beta \)-cell [36]. Besides this classical effect, TZDs may exert beneficial cardiovascular effects and protection of \( \beta \)-cell, by preserving cell mass and improving insulin secretory function [53, 54]. The Troglitazone Prevention of Diabetes (TRIPOD) study reported a marked reduction in the incidence of T2DM from 45% with placebo to 20% with troglitazone (RR = 0.45, 95% CI 0.25–0.83) in 236 overweight Hispanic women with previous gestational diabetes (age 35 years, BMI 30.5 kg/m\(^2\)) (Table 1) [55]. This effect was observed after a 2.5-year follow-up and occurred despite a modest and nonsignificant weight gain of 0.3 kg compared with placebo. The risk reduction for diabetes was also robust when only women who had IGT at baseline were considered (HR = 0.51, 95% CI 0.28–0.95). However, the nearly 33% attrition rate during follow-up is a major limitation of this study. In order to decide whether troglitazone prevents or only masks deterioration to diabetes, data of a post-trial period are interesting to analysed. Among a subset of 102 women who completed the trial without diabetes, 84 were followed for a median of 8 months after stopping study medications. At the time of post-trial testing, 6 (15%) of the placebo group and 1 (2.3%) of the troglitazone group had developed diabetes (HR: 0.13, 95% CI 0.02–1.14). After adjustment for differences in baseline and on-trial characteristics, the HR was 0.08. Thus these data suggested that protection from diabetes in the troglitazone group persisted long after...
the drug was stopped (Table 2). However, troglitazone has been withdrawn from the market because of liver toxicity [56]. The Pioglitazone in Prevention of Diabetes (PIPOD) study was conducted to evaluate β-cell function, insulin resistance, and the incidence of diabetes during treatment with pioglitazone in Hispanic women with prior gestational diabetes who had completed participation in the TRIPOD study [57].

Women were offered participation in an open study with pioglitazone (30 mg/day, uptitrated to 45 mg/day) treatment for three years and 6 months of post-drug washout. Metabolic investigation includes both oral and intravenous glucose tolerance tests. The similarity of findings between the PIPOD and TRIPOD studies supports a class effect of TZDs to enhance insulin sensitivity, reduce insulin secretory demands, and preserve pancreatic β-cell function, all in association with a relatively low rate of T2DM. The lowest rate of diabetes occurred in association with the greatest reduction in insulin secretory demands during the first year of treatment. Taken together, findings from these two trials support a role for TZDs to modify the natural history of progression to T2DM in high-risk Hispanic patients. The generalizability to other high-risk groups will require additional studies.

In a small cohort study on 172 patients with IGT and insulin resistance, a significant reduction in diabetes incidence was observed with TZD therapy (troglitazone followed by either rosiglitazone 4 mg o.d. or pioglitazone 30 mg o.d.) versus a untreated comparison group after a 3-year follow up (RR = 0.11, 95% CI 0.03–0.36) [58]. It was concluded that progression from insulin resistance and IGT to T2DM appears to be delayed or prevented with early TZD treatment.

In the US DPP [16], troglitazone (400 mg o.d.) was used initially but was discontinued during the trial for safety reason [56]. During the mean 0.9-year (range 0.5–1.5 years) of troglitazone treatment, the diabetes incidence rate was 3.0 cases/100 person-years, compared to 12.0, 6.7, and 5.1 cases/100 person-years in the placebo, metformin and intensive lifestyle participants (P < 0.001, troglitazone versus placebo and P = 0.02 troglitazone versus metformin) (Table 1) [59]. However, during the 3 years after troglitazone withdrawal, the diabetes incidence rate was almost identical to that in the placebo group (Table 2).

It was concluded that troglitazone markedly reduces the incidence of diabetes during its limited period of use, but that this action does not persist after drug withdrawal. Whether other TZD drugs used for longer periods can safely prevent diabetes remains to be determined.

The DREAM (“Diabetes Reduction Assessment with rami-pril and rosiglitazone Medication”) randomised clinical trial evaluated the effect of rosiglitazone (8 mg o.d.) versus placebo to prevent T2DM in a large cohort of 5269 individuals with IFG and/or IGT [60]. Rosiglitazone (at a maximal daily dose of 8 mg) for 3 years substantially reduced incident T2DM (RR = 0.39; 95% CI 0.34–0.45; P < 0.0001) (Table 1) and increased the likelihood of regression to normoglycaemia in adults with mild dysglycaemia at baseline (RR = 1.70; 95% CI 1.56–1.86; P < 0.0001) as compared to placebo. However, as for the first report of the DPP on metformin [16], results recently published in the original paper [60] were obtained on treatment with rosiglitazone. In the US DPP, part of the so-called prevention effect of metformin disappeared after a short period of washout of only 1–2 weeks [38]. Thus, the question whether the remarkable effect obtained with rosiglitazone in the DREAM study is a true preventing effect or only a postponing effect or even simply a masking effect remains an open question [61]. Data from a previous troglitazone trial suggested that the benefit of a TZD persists several months after the drug is stopped [55], although this durable effect was not seen in another trial [59]. Therefore, the post-trial washout data of the DREAM study were waiting with great interest [61]. They were presented at the recent International Diabetes Federation Congress early December 2006. When taking into account both the trial period and the 2.2-month washout period, the rate of progression to diabetes averaged 19.1% in the rosiglitazone group and 31.8% in the placebo group (HR = 0.53, 95% CI 0.47–0.59; P < 0.0001), compared to 11.6 versus 26.0%, respectively, at the end of the trial per se (HR = 0.40; P < 0.0001). During the washout period per se, no significant difference was observed in the progression to T2DM between the rosiglitazone arm (10.6%) and the placebo arm (9.7%; HR = 1.09, 95% CI 0.88–1.35; P = 0.44). Thus, these data provide further argument to support a true postponing or prevention effect of the thiazolidinedione rather than a specific acute treatment effect only. However, the initially planned 2–3 month washout out period may be rather short to definitely exclude a residual effect of rosiglitazone. The investigators of the DREAM study now plan to perform OGTTs 1 and 2 years after the end of the original study. Those data from this extension DREAM-ON will probably be of most interest if confirmatory results will be observed in a representative sample of individuals despite stopping the drug, as was the case in the HOPE-TOO study with ramipril [62].

As already mentioned, pioglitazone was shown to exert almost similar favourable effects compared to troglitazone in the open-label extension study of TRIPOD in women with previous gestational diabetes [57]. ACT NOW (“Actos Now for Prevention of Diabetes”) is an ongoing 45-month prospective, double-blind, randomised, placebo-controlled clinical trial that aims to recruit 600 subjects with IGT and fasting plasma glucose levels > 95 mg/dl [63]. Individuals must also have at least one additional high-risk factor for type 2 diabetes, for example family history of diabetes or a component of the metabolic syndrome. Patients receive treatment for 24 months, and during this time their fasting plasma glucose is assessed every 3 months. Their oral glucose tolerance is assessed every year and then at 45 and 51 months after treatment or if their fasting plasma glucose is ≥ 126 mg% at any visit. It is predicted that data will be available for presentation in 2008.

3.4. Acarbose

α-Glucosidase inhibitors retard carbohydrate absorption and reduce postprandial glucose responses by inhibiting α-glucosidase enzymes present on the brush border of the small intestine, which hydrolyse di- and oligosaccharides into their component monosaccharides [64]. Acarbose, although almost
not absorbed from the gut, has been reported to reduce insulin resistance, perhaps through lower postprandial plasma glucose concentrations reducing both glucose toxicity and demand on the β cell. Of the three α-glucosidase inhibitors (acarbose, miglitol and voglibose), only acarbose has been specifically evaluated in its ability to prevent or delay the progression from IGT to T2DM [65].

The STOP-NIDDM trial is an international multicentre, placebo-controlled study on the efficacy of acarbose in preventing or delaying the development of T2DM in a population with IGT [66]. A total of 1429 subjects (age 55 years, BMI 31 kg/m²) diagnosed with IGT and having a fasting plasma glucose concentration ≥ 5.6 mmol/l were randomised in a double-blind fashion to receive either acarbose (100 mg t.i.d., n = 714) or placebo (n = 715) for a predictive median follow-up period of 3.9 years. The primary outcome is the development of T2DM diagnosed using a 75-g OGTT. The final analysis of the data regarding primary endpoint showed that 221 (32%) patients randomised to acarbose versus 285 (42%) randomised to placebo developed diabetes (RR = 0.75; 95% CI 0.63–0.90; P = 0.0015) (Table 1). Despite the small weight loss in the acarbose group probably contributed to delaying onset of diabetes, acarbose was still effective after adjustment for weight loss (P = 0.0063). The results suggest that 11 patients with IGT would need to be treated for 3.3 years to prevent one event of development of diabetes. Post-hoc subgroup analyses also indicated that acarbose effectively reduced risk of developing T2DM irrespective of age, sex, and BMI. If the diagnosis of diabetes was based on 2 OGTTs as recommended by the Expert Committee of the American Diabetes Association [8], acarbose treatment resulted in an even greater 36.4% reduction in the incidence of diabetes (P = 0.0003). Furthermore, acarbose significantly increased reversion of IGT to normal glucose tolerance (P < 0.0001). At the end of the study, treatment with placebo for 3 months was associated with an increase in conversion of IGT to diabetes (47 of 306 in the group originally assigned to acarbose versus 21 of 199 in the group originally assigned to placebo), an observation which again suggests that long-term treatment may be mandatory to prevent diabetes in such at risk patients (Table 2) [67]. It is noteworthy that almost a quarter of patients discontinued early, of whom 48% discontinued during the first year, mostly because of gastrointestinal side-effects. Although the molecular mechanisms still need investigation, it was concluded that acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay development of T2DM in patients with IGT, especially since the drug has no toxic effects. These conclusions were challenged in a “for debate” paper suggesting that the validity of the results of the STOP-NIDDM trial is seriously flawed, because of selection bias, inadequate blinding, and bias in data analysis and reporting [68]. However, the authors confirmed that the trial results are scientifically sound and credible. The investigators stand strongly behind these results demonstrating that acarbose treatment is associated with a delay in the development of T2DM (as well as hypertension and cardiovascular complications) in a high-risk population with IGT [69].

In the Chinese DPS, subjects with mild overweight (BMI: 25 kg/m²) and IGT were divided into a control group (n = 85) which received conventional education, a metformin group (n = 88) (see above) and an acarbose group (n = 88) [39]. Over a 3-year period, 34.9% in the control group versus 6.0% in the acarbose group progressed to diabetes. This represents an impressive risk reduction of 87.8% for acarbose. However, these remarkable results were only partially confirmed in an UK trial, the EDIT [40]. Indeed, primary analyses showed no significant difference in RR for T2DM between the control group and the acarbose group after a mean 6-year follow-up (RR = 1.04; P = 0.81). However, in those patients with IGT at baseline (i.e. similar population as that included in the STOP-NIDDM or in the Chinese DPS), RR of conversion to T2DM was reduced significantly with acarbose (RR = 0.66; P = 0.046) [40]. Even if the number of patients in the treatment group was rather small and might be underpowered to show a significant difference, it was not smaller, but rather slightly higher, as compared to the Chinese DPS [39]. An already mentioned similar discrepancy between the two trials was observed as far as the effect of metformin on diabetes prevention is concerned. The reasons for such discrepancies are not clear, but may result from the different designs of the two studies, i.e. a randomised controlled trial in EDIT versus a cohort study in the Chinese DPS. According to a recent Cochrane systematic review [70], there is evidence that acarbose reduces the incidence of T2DM in patients with IGT. However, it is unclear whether this should be seen as prevention, delay or masking of diabetes.

3.5. Insulin

The ORIGIN study is an international randomised placebo-controlled trial examining the efficacy of insulin glargine (and/or omega 3 in a 2 × 2 factorial design) in decreasing the risk of cardiovascular events in 10,000 subjects followed for 5 years [71]. Participants must be 50 years or older with elevated blood glucose levels (mild T2DM, IFG, or IGT) and history of cardiovascular disease (including but not limited to heart attack, stroke, or angina). As a secondary objective, investigators will look at the effect of glargine (and/or omega 3) on the development of T2DM whose diagnosis will be based on OGTT (however, only 19% of the population have IFG and/or IGT at baseline). It is the only trial that will assess early intervention with insulin in patients with IGT and/or IFG. The results should be available in 2009.

4. Discussion

An extensive analysis of the data published in the literature shows that the administration of a glucose-lowering agent, as compared to placebo, is able to reduce the incidence of new diabetes in individuals with IGT and/or IFG. Positive results were reported with metformin, glitazones and acarbose. The reduction in the incidence of T2DM obtained with oral antidiabetic agents is greater than that observed with other pharmacological approaches [23], and indeed seems to be much the same.
(around 60%) with glitazones than with intensive lifestyle intervention [15,16]. However, part of the beneficial effects was lost during a rather short-term wash-out period of 1–2 weeks up to 2–3 months, raising the question about a real prevention effect of the drug [30,31,61,67]. Data concerning sulphonylureas are more heterogeneous and often disappointing, so that the results with the new prandial insulin secretagogue nateglinide currently evaluated in the NAVIGATOR trial are awaited with interest [51].

Most of the trials performed with metformin gave positive results, despite some heterogeneity. The largest and most interesting trial was the US DPP study demonstrating a 31% RR reduction in the incidence of diabetes, an effect particularly marked in obese and young individuals with IGT [16]. However, part of the effect disappeared after a short washout period of 1–2 weeks only [38]. Because of the mode of action of metformin [34] and its pharmacokinetics characteristics [72], one could not definitely exclude a residual masking effect [31]. The question appears crucial as a short administration of one could not definitely exclude a residual masking effect [31].

The place of insulin secretagogues, especially sulphonylureas, in the prevention of T2DM is not obvious yet. The timing of glucose tolerance evaluation after the last dose of ingested insulin secretagogue agent is even more crucial than for metformin because of the more rapid acute action of such compounds on insulin secretion and glucose tolerance. While results with sulphonylureas were rather disappointing, new hope arises with the use of prandial insulin secretagogues (gli-nides), which more specifically target post-meal hyperglycaemia while limiting the risk of hypoglycaemia [50]. The rationale behind this concept is that a better control of postprandial hyperglycaemia by stimulating early insulin secretion will globally reduce the stress on the β-cells. If the results from the NAVIGATOR trial are positive, i.e. reduced incidence of new onset diabetes with a good safety profile, the use of a short-acting prandial insulin secretagogue as nateglinide will offer a new alternative for the prevention of T2DM in high-risk individuals [51]. However, the natural history of T2DM is characterised by a decline in β-cell mass/function. Therefore, agents that may potentially reverse this process would be of great interest for both the prevention and treatment of T2DM [79]. In this respect, new agents capable of stimulating insulin secretion and possibly protecting and even regenerating β-cell as well, such as glucagon-like peptide-1 (GLP-1) analogues and dipeptidylpeptidase-IV (DDP-IV) inhibitors, offer new exciting perspectives [80,81]. However, the cost of these new drugs will probably be much higher and there are no clinical trials available (or ongoing) demonstrating their interest in the prevention of T2DM yet.

Currently available data suggest that glitazones are the most promising drugs for the prevention of T2DM. Besides their insulin sensitising effect [52], TZDs may exert protection of β-cell, by preserving cell mass and improving insulin secretory function, as shown in animal models and suggested by preliminary studies in humans [53,54,79]. Results from clinical trials are also encouraging. Indeed, they demonstrate the greatest reduction of the incidence of T2DM, much the same as that observed with intensive lifestyle intervention [15,16]. A sustained effect may be expected [55], although conflicting results have been reported [59]. To answer this crucial question, data from the wash-out period of the DREAM trial are of major interest. The recently reported results are reassuring as a significant reduction in the progression towards T2DM remained after the 2.2-month washout period of rosiglitazone and no...
immediate rebound in the development of T2DM was observed soon after stopping the thiazolidinedione as compared to placebo. Although the washout period was too short to provide definitive evidence, these data may support a disease-modifying effect rather than a pure treatment effect. However, even if positive, the rather high cost of such pharmacological approach and the possible occurrence of adverse effects (weight gain, fluid retention, congestive heart failure) may limit the use of TZDs in this indication in the future, especially if high dosage (as in the DREAM trial) is recommended [61]. One alternative to increase the efficacy while improving the cost-effectiveness might be to use combination pharmacological therapy such as rosiglitazone plus metformin, in addition to a healthy lifestyle programme, as currently evaluated in the CANOE study in subjects with IGT [78].

Acarbose, because of its absence of toxicity and its efficacy to prevent T2DM in individuals with IGT in the STOP-NIDDM trial [66], appears to be a valuable alternative, although not all clinical trials provided clear-cut results [70]. While indirect comparison between US DPP results with metformin [16] and STOP-NIDDM results with acarbose [66] suggests a slightly greater protective effect of the former compound than the latter, preliminary observations of the UK EDIT trial seems to indicate a more potent preventive effect of acarbose than of metformin in a direct comparative trial [40]. What ever, the cost of the drug, although considered as acceptable when considering the prevention of both diabetes and cardiovascular events [82], and its rather poor gastrointestinal tolerance may represent limitations to use acarbose only for prevention, so that the drug should probably also be considered only for high-risk individuals.

Interestingly, the ORIGIN trial randomised people with IFG/IGT or mild diabetes [71], thus providing further arguments to support the view that type 2 diabetes is probably a continuum from IGT/IFG to overt fasting hyperglycaemia [3, 43,83–85]. Indeed, in all the previous trials having assessed the efficacy of oral antidiabetic drugs in patients with IGT and/or IFG, the question arises whether the proposed pharmacological interventions should be considered as an early treatment of the disease rather than a strategy of prevention stricto sensu. There is growing evidence that appropriate management of T2DM should be initiated at an earlier stage, certainly when fasting hyperglycaemia overcomes the threshold of 126 mg/dl (7 mmol/l) defining diabetes, but also probably even at an earlier stage in individuals with IGT and/or IFG. Of course, the crucial question is to decide if pharmacological intervention should be recommended at this stage, considering the well demonstrated potential of lifestyle interventions.

A major objective in the future will be to compare the clinical outcomes and cost-effectiveness of all these strategies for managing people at high-risk for diabetes, especially pharmacological approaches with intensive lifestyle intervention [74, 76]. As recently emphasized [61,86], the demonstration of the durability of the effect obtained with pharmacological intervention appears to be crucial since recent observations from the Finnish Diabetes Prevention study suggested that prevention of type 2 diabetes with intensive lifestyle is sustained, at least for several years [83,87]. We need to decide whether we want to spend more on drugs for prevention rather than on lifestyle measures and public health strategies to reduce the burden of T2DM in adults [86]. Finally, because of the rise in the prevalence of obesity and T2DM in children and adolescents, another challenge will be the implementation of new approaches to prevent T2DM in young people, especially in high-risk groups [88]. Obviously, prevention strategies should focus here on environmental changes favouring a healthier life. Presently, limited pharmacotherapeutic options need to be expanded for the prevention of T2DM in childhood. Evidence-based research and clinical experience in pediatrics, possibly modelled after adult trials, need to be developed before considering drug therapy as a possible mean to prevent T2DM in children and adolescents [24,88].

5. Conclusion

The goal of ultimately reducing the population burden of diabetes by early treatment and prevention is clearly of pivotal importance. Obviously, intensive lifestyle intervention is the mainstay for the prevention of T2DM given the remarkable reduction in the incidence of T2DM, the prolonged benefits, the demonstrable cost-effectiveness and the absence of adverse events. Unfortunately, intensive lifestyle intervention is difficult to implement and to sustain in most individuals and many subjects will still progress to T2DM. Besides lifestyle modifications, pharmacological strategies might be considered as a valuable alternative. Owing to the pathophysiology of T2DM, these drugs must act either by reducing insulin resistance and/or by improving insulin secretion, with a special interest in the protection of β cells. As far as glucose-lowering agents are concerned, an at least partial masking effect should be excluded because most results were obtained either when subjects were on the drug or after a rather short washout period. In addition, because T2DM is a progressive disease, it remains to be established in long-term studies whether the so-called preventing effect is not simply a postponing effect. Anyway, results from prevention studies in subjects with IGT and/or IFG demonstrate that various oral antidiabetic agents are able to improve glucose tolerance at an initial stage of the disease while being well-tolerated. These observations provide further arguments for early pharmacological therapy in very high-risk individuals in order to tackle the progression of T2DM whose natural history is well known.

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