Advances in the treatment of prediabetes

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***Abstract*:** Type 2 diabetes mellitus (T2DM) is epidemic in most developed and many developing countries. Owing to the associated morbidity, mortality and high costs of care, T2DM is an important global public health challenge and target for prevention. Patients at high risk for T2DM (referred to as having prediabetes) can be easily identified based on fasting glucose levels or responses to an oral glucose tolerance test (OGTT). More recently, glycosylated hemoglobin (i.e. HbA1c, which is also termed A1C in the US) has also been introduced as a diagnostic tool for both prediabetes and diabetes. Such patients are also at risk for cardiovascular disease (CVD). Since obesity and physical inactivity are important risk factors for T2DM, lifestyle interventions, emphasizing modest weight loss and increases in physical activity, should be recommended for most patients with prediabetes. Such interventions are safe and effective and also reduce risk factors for CVD. A number of oral antidiabetic agents have been shown to be effective at delaying onset of T2DM in patients with prediabetes. Thiazolidinediones (TZDs) are the most effective, reducing incident diabetes by up to 80%. Metformin, acarbose and orlistat also reduce incident diabetes, but their efficacy is much lower than the TZDs. Pharmacologic interventions may be appropriate for patients at particular risk for developing diabetes, but the benefits of treatment need to be balanced against the safety and tolerability of the intervention. If pharmacologic treatment is warranted, metformin should be considered first because of its favorable overall safety, tolerability, efficacy and cost profile.

***Keywords*:** cardiovascular disease, obesity, prediabetes, type 2 diabetes

Introduction

An epidemic of diabetes threatens the health of large numbers of individuals in developed and developing countries alike [Shaw *et al.* 2010; King *et al.* 1998]. Diabetes is associated with serious microvascular (i.e. neuropathy, nephropathy and retinopathy), and macrovascular complications [Matfin, 2009]. In particular, diabetes is a potent risk factor for cardiovascular disease (CVD, risk increased fourfold) and this complication accounts for much of the excess morbidity, mortality and costs of care associated with diabetes. Thus, diabetes represents a critical public health challenge and an important target for prevention efforts.

Most of the recent growth in the prevalence of diabetes can be attributed to increases in type 2 diabetes mellitus (T2DM), which now accounts for ~95% of all cases [American Diabetes Association, 2010; Matfin, 2009]. Although it is clear that a genetic predisposition contributes to T2DM, the epidemic of diabetes has largely been driven by societal and environmental changes that promote physical inactivity and obesity, increasing risk for T2DM [American Diabetes Association, 2010; Shaw *et al.* 2010; Matfin, 2009]. Obesity is considered responsible for ~60% of T2DM worldwide. Indeed the common association of diabetes and obesity has been termed '*diabesity*'.

The pathophysiology of T2DM has been well studied in recent years and is similar in most populations [Abdul-Ghani and DeFronzo, 2009; DeFronzo, 2007; Pratley and Weyer, 2001; Weyer *et al.* 1999; Pratley, 1998]. Insulin resistance and impaired insulin secretion are key features, preceding and predicting the development of T2DM [Abdul-Ghani and DeFronzo, 2009; DeFronzo, 2007; Pratley and Weyer, 2001; Weyer *et al.* 1999; Pratley, 1998]. Progression to overt diabetes from a prediabetes state occurs gradually over a period of many years

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and is characterized by worsening insulin resistance and insulin secretory dysfunction and gradual increases in fasting and postprandial plasma glucose concentrations [Abdul-Ghani and DeFronzo, 2009; DeFronzo, 2007; Pratley and Weyer, 2001; Weyer *et al.* 1999; Pratley, 1998]. More recently, it has been shown that β-cell failure occurs much earlier in the natural history of T2DM and is more severe than previously thought. In a metabolic study of prediabetes subjects, those in the upper-tertile of glucose values in the impaired glucose tolerance (IGT) category were already maximally insulin resistant and had lost over 80% of their β-cell function. The resulting increases in plasma glucose allow individuals at high risk of T2DM to be easily identified using simple and widely available clinical measures.

Definition of diabetes and prediabetes

Normal glucose tolerance (NGT), diabetes and the categories of increased risk for diabetes (i.e. prediabetes) are defined in Table 1 [American Diabetes Association, 2010; International Expert Committee, 2009; Nathan *et al.* 2007].

Patients at high risk for T2DM can be identified based on fasting glucose levels (i.e. impaired fasting glucose [IFG]) or postprandial responses to an oral glucose challenge (i.e. IGT). More recently, glycosylated hemoglobin (i.e. HbA1c, which is also termed A1C in the US) has also been introduced as a diagnostic tool for both pre-diabetes (A1C 5.7–6.4%) and diabetes (A1C ≥6.5%) [American Diabetes Association, 2010; International Expert Committee, 2009].

Epidemiology of prediabetes

Prediabetes is a common disorder in most populations [Nathan *et al.* 2007]. The reported prevalence of prediabetes varies widely from study to study, in part because of evolving definitions of prediabetes but also because IFG and IGT appear to vary among populations with different ethnic backgrounds [Cowie *et al.* 2006; Shaw *et al.* 1999; Ko *et al.* 1998]. Recent data from the US indicate that the prevalence of IFG is ~26% and that of IGT is ~15% in the adult population [Cowie *et al.* 2006]. Both IFG and IGT increase in prevalence with age [Shaw *et al.* 1999]. Although there is some overlap between IFG and IGT, most studies have shown that these criteria define different populations at risk for T2DM and other complications (i.e. CVD) [Cowie *et al.* 2006; Shaw *et al.* 1999; Ko *et al.* 1998].

Risk of developing diabetes

The progression of prediabetes to T2DM has been examined in a number of populations with varying results. In general, epidemiological studies indicate that ~25% of subjects with IFG or IGT progress to T2DM in 5 years, whereas about ~50% remain prediabetic and ~25% revert to normal [Larson *et al.* 2004]. Several recent prospective studies have suggested that the rate of progression to T2DM may be even higher, averaging ~10–12% per year [Knowler *et al.* 2002; Tuomilehto *et al.* 2001; Pan *et al.* 1997].

Risk of developing cardiovascular disease

A large number of studies have demonstrated that diabetes *per se* markedly increases risk for CVD [Kannel and McGee, 1979]. This is due, in part, to a higher prevalence of traditional cardiovascular (CV) risk factors, such as hypertension and dyslipidemia, among patients with T2DM (i.e. many of these patients have the metabolic syndrome). However, even after controlling for these risk factors, T2DM is associated with a two- to fourfold higher risk of CVD.

Table 1. Classification of glucose tolerance.

Criteria	FPG Level (mmol/L [mg/dl])	2-h PG Level (mmol/L [mg/dl])	HbA1c (also termed A1C) (%)
NGT	<5.6 [<100]	<7.8 [<140]	
Prediabetes: IFG*	5.6–6.9 [100–125]	<11.1 [<200]	
Prediabetes: IGT*	<7.0 [<126]	7.8–11.1 [140–199]	
Prediabetes: HbA1c (also termed A1C)*			5.7–6.4
Diabetes	≥7.0 [≥126]	≥11.1 [≥200]	≥6.5

Categories of increased risk for diabetes (i.e. prediabetes) include: impaired fasting glucose (IFG)*, impaired glucose tolerance (IGT)* and HbA1c (also termed A1C)* of 5.7–6.4%. NGT denotes normal glucose tolerance.

Numerous longitudinal studies indicate that there is a linear relationship between both fasting and postprandial glucose concentrations and CVD [Coutinho *et al.* 1999]. This risk extends into the nondiabetic range and is somewhat stronger for postprandial than fasting glucose concentrations. Not surprisingly, IFG and IGT are associated with a modestly increased risk for CVD (hazard ratio ~1.1–1.4), but IGT may be a slightly better predictor [DECODE, 2001].

Rationale for the prevention of diabetes

A diagnosis of prediabetes identifies an individual at high risk of developing T2DM and at increased risk of CVD. There are several reasons why treating pre-diabetes to prevent progression to overt T2DM might be beneficial, as outlined in Table 2 [Nathan *et al.* 2007].

The microvascular complications (i.e. neuropathy, retinopathy and nephropathy) related to diabetes result in considerable morbidity and mortality. Glycemic control, diabetes duration, hypertension, hyperlipidemia and smoking remain important risk factors. Historically, it was felt that the complications of diabetes followed the diagnosis of diabetes. However, a number of population and patient-based studies have shown that the complications of diabetes can develop prior to the diagnosis of diabetes and can occur in ~5–10% of prediabetes subjects [DeFronzo, 2007; Dunstan *et al.* 2004]. The AusDiab studies, a population-based survey of 11,247 adults aged over 25 years, used an oral glucose tolerance test (OGTT) to stratify subjects into those with diabetes (7%), IFG or IGT (16%), or NGT (76%) [Dunstan *et al.* 2004]. Surprisingly, 22% of individuals with prediabetes (IGT and/or IFG) had at least one microvascular complication.

Table 2. Rationale for preventing diabetes.

- Prevention of microvascular complications
  - Retinopathy
  - Nephropathy
  - Neuropathy
  - Amputations
- Prevention of macrovascular complications
  - Coronary artery disease
  - Congestive heart failure
  - Stroke
  - Peripheral vascular disease
- Changing the natural history of diabetes
  - Improving islet function
  - Simplified treatment and monitoring regimens
  - Decreasing polypharmacy

Follow up analysis of the DCCT study cohort in type 1 diabetes mellitus (T1DM) subjects has shown that the benefits of 6.5 years of intensive glycemic control on neuropathy, extended for at least 8 years beyond the end of the DCCT, similar to the findings described for retinopathy and nephropathy [Nathan *et al.* 2005]. This is referred to as 'metabolic memory' or the so-called 'legacy effect'. More recently, similar findings have been described in the 10-year follow-up of the intensively treated group of the T2DM subjects in the United Kingdom Prospective Diabetes Study (UKPDS) [Holman *et al.* 2008]. It is presumed that early detection and treatment of prediabetes may also result in long-term benefit with respect to preventing or reducing complications (i.e. by inducing the 'legacy effect').

Lifestyle interventions to prevent T2DM

Obesity is the most potent acquired risk factor for T2DM. The age-adjusted relative risk of developing T2DM is ~10-fold higher for men with a BMI of 30 kg/m^2 relative to men with a BMI of <23 kg/m^2 and the risk is even higher for women, in whom a BMI of 30 kg/m^2 is associated with a ~30-fold higher risk [Colditz *et al.* 1995; Chan *et al.* 1994]. Other studies have demonstrated that physical inactivity and a high-fat, low-fiber diet are additional risk factors for T2DM [Hamman *et al.* 2006; Parillo and Ricardi, 2004]. Thus, a number of recent studies have examined the efficacy of lifestyle interventions on preventing T2DM in subjects with prediabetes.

The Da Qing study demonstrated that community-based diet and exercise interventions reduced incident T2DM by 30–40% among Chinese subjects with IGT who were followed for 6 years [Pan *et al.* 1997]. The US Diabetes Prevention Program (DPP) study found that an intensive diet and exercise intervention reduced incident T2DM by 58% among 1079 subjects with IGT followed an average of 2.8 years compared with a control group who received only brief lifestyle advice and placebo ($n = 1082$) [Knowler *et al.* 2002]. A similar study in Asian Indians (the Indian Diabetes Prevention Program [IDPP]) reported a 28% reduction in incident T2DM over 30 months in 133 subjects who received a lifestyle modification intervention compared with controls [Ramachandran *et al.* 2006]. The Finnish Diabetes Prevention Study (FDPS) demonstrated a 58% reduction in T2DM over a

median of 4 years in 265 subjects randomized to a diet and exercise lifestyle intervention compared with 257 subjects who received conventional care [Tuomilehto *et al.* 2001]. More recently, 3-year median follow-up data on the FDPS subjects revealed a prolonged decreased risk (43% reduction in T2DM) in the former intervention group compared with conventional care [Lindstrom *et al.* 2006]. This demonstrates that lifestyle intervention in individuals at high risk for T2DM not only reduces diabetes risk in the short-term when the actual intervention is carried out, but also that effects on lifestyle change and diabetes risk are long term. This finding was also confirmed in the DPP outcomes study (DPPOS) which showed durable improvements of lifestyle intervention for up to 10 years [Diabetes Prevention Program Research Group, 2009]. In an additional analysis of the DPP, weight reduction (as opposed to increased exercise or reduction in dietary fat) was the most important element of the lifestyle intervention for preventing progression to T2DM [Hamman *et al.* 2006].

In addition to reducing new cases of T2DM, lifestyle interventions are typically associated with improvements in other CV risk factors such as blood pressure (BP), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels [Goldberg *et al.* 2009; Orchard *et al.* 2005]. In the DPP study, metabolic syndrome was diagnosed in approximately half of the participants at baseline. In subjects with the metabolic syndrome at baseline, 23% of the metformin group and 38% of the lifestyle group had resolution of the diagnosis of the metabolic syndrome by the end of the study [Orchard *et al.* 2005]. In addition, both lifestyle and metformin therapy also subsequently reduced the development of metabolic syndrome in the remaining participants without the syndrome at baseline [Orchard *et al.* 2005]. Collectively, these studies demonstrate that lifestyle modification is a safe and very effective approach to preventing T2DM and reducing CV risk in patients with prediabetes (i.e. in part by prevention or treatment of metabolic syndrome). Importantly, none of these studies was powered to detect effects on CVD outcomes.

Pharmacologic interventions to prevent T2DM

Although lifestyle modification is a highly effective approach to preventing T2DM, the programs implemented in the studies discussed above required personnel (dieticians, exercise physiologists, behavioral therapists) and resources beyond those available in most clinics. In addition, such lifestyle interventions are notoriously difficult to maintain over the long term. Owing to this, a number of pharmacological interventions to prevent T2DM have also been studied. Many of the pharmacological interventions tested to prevent diabetes are also the same as therapies used to treat established diabetes.

Several large, well-powered trials have reported beneficial effects of various drugs. The DPP discussed above demonstrated that metformin (850 mg twice a day, $n = 1073$) decreased incident T2DM by 31% relative to control subjects who received placebo [Knowler *et al.* 2002]. Similarly, the IDPP reported a 26% reduction in incident T2DM in 120 patients treated with metformin at a lower dose (250 mg twice a day) relative to placebo [Ramachandran *et al.* 2006]. More recently, the DPPOS trial showed durable improvements of metformin therapy for up to 10 years [Diabetes Prevention Program Research Group, 2009]. The STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial, which randomized 1429 subjects with IGT to acarbose (100 mg three times a day with meals) or placebo, demonstrated that acarbose treatment reduced incident T2DM in subjects with IGT by 25% relative to controls [Chiasson *et al.* 2002]. The XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects) trial examined the efficacy of orlistat, a gastrointestinal lipase inhibitor, on incident T2DM in 3305 obese subjects followed for 4 years [Torgerson *et al.* 2004]. In contrast to most other studies, subjects with both NGT (~79% of the study population) and IGT (~21% of the study population) were enrolled. In the trial as a whole, orlistat (120 mg three times daily) decreased incident T2DM by 37%.

Several studies have examined the efficacy of insulin-sensitizing TZD drugs in preventing T2DM. In the DPP, subjects randomized to troglitazone (400 mg per day, $n = 585$) had a 75% reduction in new diabetes over an average of 9 months of treatment [Knowler *et al.* 2005]. Owing to hepatoxicity, this drug was removed from the trial prematurely, before subsequently being withdrawn from clinical use altogether. The TRIPOD (Troglitazone in Prevention of Diabetes) study conducted in women with prior gestational diabetes (who normally have a ~50%

5-year risk of progressing to T2DM) demonstrated that troglitazone decreased the risk for diabetes by 55% relative to placebo over a median follow up of 30 months [Buchanan *et al.* 2002]. This study was also terminated prematurely when troglitazone was withdrawn from the market. However, the open-label follow-up PIPOD (Pioglitazone in Prevention of Diabetes) study, which used pioglitazone instead of troglitazone, demonstrated similar findings (i.e. 62% reduction).

The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) trial evaluated the efficacy of rosiglitazone in preventing T2DM [DREAM, 2006a]. In this study, 5269 subjects with IGT and/or IFG were randomized to treatment with rosiglitazone (8 mg per day) or placebo and followed them for a median of 3 years. Rosiglitazone reduced incident diabetes by 60% relative to placebo and, importantly was effective in both subjects with IFG and IGT. More recently, the ACT NOW (Actos Now for prevention of diabetes) trial compared the effects of the TZD pioglitazone versus placebo in 602 patients with IGT [DeFronzo *et al*. 2009]. The results showed an impressive 81% reduction in the conversion of IGT to T2DM.

Drugs that do not primarily target hyperglycemia may also reduce the risk for T2DM. Secondary and post-hoc analyses of a large number of trials of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) for various CV indications suggest that these drugs could reduce risk for T2DM by as much as 25% [Scheen, 2004]. This was tested prospectively in the DREAM trial, which randomized patients to ramipril (15 mg per day) versus placebo (in addition to rosiglitazone) in a 2×2 factorial design [DREAM, 2006b]. In contrast to earlier studies, ramipril did not significantly decrease the incidence of new diabetes, although there was a trend for a beneficial effect. More recently, the NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) study group published the 2×2 factorial design trial examining the effects of nateglinide, a short-acting insulin secretagogue, and valsartan, an ARB, in 9306 patients with IGT and either CVD or CV risk factors [NAVIGATOR study group, 2010a; NAVIGATOR study group, 2010b; Califf et al. 2008]. This was the first study initiated in prediabetes with the primary aim of determining whether the interventions actually prevented CVD events. Unfortunately, both drugs (nor the combination) reduced the coprimary CVD outcomes. The only positive result was a weak reduction in the incidence of diabetes (other coprimary endpoint) with valsartan (relative reduction of 14%) over a mean follow-up of 5 years [NAVIGATOR study group, 2010b].

A common feature of most pharmacological interventions is that adherence to treatment is relatively poor. In the STOP-NIDDM and XENDOS trials, 30% and 48% of subjects, respectively, failed to complete the active intervention, whereas in the DPP and DREAM trials, adherence to metformin and rosiglitazone was only about 70% [DREAM, 2006a; Torgerson *et al.* 2004; Chiasson *et al.* 2002; Knowler *et al.* 2002]. In part, low rates of compliance may be due to the poor tolerability of some of the drugs, and in part it might be that patients with prediabetes who are asymptomatic stop taking the medications because they fail to experience tangible benefits.

What have these studies told us about the benefits of prevention?

To date, no drug has received an indication for diabetes prevention. In part, this is because of uncertainty about whether there is a clinical benefit in preventing diabetes. At the simplest level, the natural history of both IGT and IFG is defined by worsening hyperglycemia. A final definition of 'natural history' encompasses the complications of hyperglycemia, including microvascular and macrovascular disease. Generally speaking, the risk of microvascular complications associated with IGT/IFG and early diabetes is small (~5–10% overall) [DeFronzo, 2007; Coutinho *et al.* 1999]. Therefore, robust prospective studies that have examined the effect of interventions on this aspect of the natural history of IGT/IFG have not been performed. Nor have any of the diabetes prevention studies completed to date been powered to detect effects of the intervention on CV events. In the DPP, metformin treatment had minimal effects on BP and dyslipidemia; however, it did reduce the number of subjects categorized as having metabolic syndrome [Orchard *et al.* 2005]. In the STOP-NIDDM trial, significant reductions in incident hypertension and MI were seen with acarbose treatment, although the number of events was very small [Chaisson *et al.* 2003]. In addition, treatment with acarbose seemed to delay progression of carotid artery intima-media

thickness (CIMT), a surrogate measure of atherosclerosis [Hanefeld *et al.* 2004]. CIMT was also measured in the TRIPOD study and progression was decreased with troglitazone [Xiang *et al.* 2005]. Although the DREAM trial was a relatively large trial, the population was selected to be at low risk for CVD and neither treatment with rosiglitazone nor treatment with ramipril decreased CV events. In comparison, the NAVIGATOR study was specifically targeting patients with IGT and either existing CVD or CV risk factors [NAVIGATOR study group, 2010a; NAVIGATOR study group, 2010b; Califf et al. 2008]. Unfortunately, both nateglinide and valsartan (nor the combination) reduced the coprimary CVD outcomes. A number of study issues including nonadherence, high rates of loss of follow-up, and use of off-study ACE-inhibitors in the placebo group, may explain the lack of positive effect on CVD outcomes [Nathan, 2010]. Thus, at present it is not possible to say whether interventions that alter the natural history of the progression of prediabetes to diabetes also affect the development of microvascular complications and CVD.

The clinical benefit of glucose lowering in diabetes is well established, but whether delaying or preventing progression to T2DM will also result in a benefit in such outcomes is not known [Holman *et al.* 2008; Nathan *et al.* 2005; UKPDS, 1998]. Until such benefit can be established, it is unlikely that any drugs will receive approval by the US Food and Drug Administration (FDA) or other regulatory authorities for the prevention of T2DM.

Regulatory guidance on prevention of T2DM

Several other concerns exist for the regulators regarding approval of drugs for the prevention of T2DM. These include the exposure of many patients to drugs when they may not need them, because they would have been unlikely to convert to T2DM anyway (at least in the short term); and also the balance of benefit and harm for prediabetes is completely different from that for T2DM, necessitating more inertia for using drug therapy.

The FDA have recently issued draft guidance on the rationale and suggested clinical development for drugs seeking marketing approval for the prevention of T2DM [FDA, 2009].

In phase 3 studies for drugs intended to prevent the development of T2DM in high-risk individuals (such as individuals with IGT and/or IFG, or with a history of gestational diabetes), potential endpoints supporting approval include delay in T2DM diagnosis or reduction in the proportion of patients diagnosed with T2DM by acceptable criteria (e.g. American Diabetes Association [ADA], World Health Organization [WHO]), relative to placebo. These study designs should include a follow-up (washout) period to assess whether the tested agent truly delays progression to diabetes or only masks diabetes during the treatment period. Such studies will likely be of substantial duration (i.e. 2–4 years) and size (e.g. thousands of subjects).

For prevention studies of drugs with a pharmacological action of improving glycemic parameters (e.g. approved treatments used in the prevention setting), improvement in clinical parameters beyond those that would be expected from glucose lowering alone should be demonstrated, since the forestalling of a biochemical diagnosis of frank diabetes from the prediabetes state may not itself be a sufficiently tangible benefit against which one can appropriately judge the risks. Such supportive evidence can include demonstration of a durable delay in the onset of T2DM after the prevention therapy is stopped, or can show that the delay in progression to T2DM is accompanied by other indicators of clinical benefit (e.g. delay or lessening in microvascular or macrovascular complications). That said, the more modest the treatment effect, the higher the standard for safety and the more restricted (e.g. to subjects at highest risk for near-term conversion to frank T2DM) the indicated target population.

Despite no current agents being approved for prediabetes to T2DM progression, the recent results from the ACT NOW study using pioglitazone were extremely impressive (i.e. 81% reduction in progression) and will likely result in a supplemental New Drug Application (sNDA) by the sponsors in the near future [DeFronzo *et al.* 2009].

Ongoing diabetes prevention trials and future prospects

In addition to the trials described above, several large diabetes prevention trials are ongoing. The ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial is a 2×2 factorial

design trial examining the effects of glargine, a long-acting insulin analogue, and omega-3 polyunsaturated fatty acids on CVD end points in 12,500 patients with IFG, IGT and early T2DM [Schwartz, 2006]. Progression to T2DM is a secondary end point in the ORIGIN study.

A new class of oral antidiabetic agents called dipeptidyl-peptidase (DPP)-4 inhibitors are either in early development or on the market [Drucker and Nauck, 2006; Pratley *et al.* 2006; Deacon *et al.* 2004]. These agents act by augmenting endogenous levels of active glucagon-like peptide-1 (GLP-1) and are particularly attractive for the prevention of T2DM because they enhance insulin secretion in a glucose-dependent manner and, thus, do not provoke hypoglycemia. As a class, they seem to be very well tolerated and do not cause gastrointestinal complaints, weight gain or edema. Moreover, animal studies suggest that DPP-4 inhibitors improve β-cell mass, so these agents may exhibit true 'disease modification' properties [Drucker and Nauck, 2006; Deacon *et al.* 2004].

Also on the horizon for the prevention of diabetes are studies of GLP-1 agonists [Drucker and Nauck, 2006]. Exenatide (twice-daily injection) was the first of this novel class of drugs to be approved for the treatment of diabetes [Drucker and Nauck, 2006]. More recently, liraglutide (once-daily injection) has also been approved for the treatment of diabetes [Drucker and Nauck, 2006]. However, initial and more robust clinical data suggest that these agents cause significant weight loss in addition to the glucose-lowering effects [Bray, 2009; Drucker and Nauck, 2006]. Thus, they might reasonably be anticipated to decrease incident diabetes through both weight loss and direct beneficial metabolic effects. The major limiting factor for putative role of GLP-1 agonists in the prevention of diabetes is the need for daily injections which may result in patient adherence problems. However, this may be overcome by the introduction of long-acting GLP-1 agonist formulations requiring weekly or monthly injection, which are in late-stage clinical development [Drucker and Nauck, 2006].

Several other therapies are also currently under investigation for the treatment of prediabetes. These include the bile acid sequestrant, colesevelam, which is already approved as an antidiabetic agent [Jones *et al.* 2009]. A number of studies indicate that there is a relationship between low vitamin D levels and prediabetes [Barengolts, 2010]. Small clinical trials suggest beneficial effect of vitamin D supplementation in prediabetes including improved insulin secretion and insulin sensitivity. In addition, vitamin D deficiency activates the renin–angiotensin–aldosterone pathway and can predispose to hypertension, increased insulin resistance and inflammation, leading to increased CVD risk.

Collectively, results from these studies should greatly enhance our understanding of the natural history of prediabetes. Of critical importance, studies reporting in the next few years will rigorously test whether preventing diabetes improves clinical outcomes. While both IGT and IFG are associated with a similar risk for progression to T2DM, there are metabolic differences in the two conditions that might imply a different natural history with respect to insulin resistance and β-cell decompensation. It will be important in the future to determine whether certain interventions are best targeted toward specific metabolic phenotypes, such as IFG or IGT. There is a need for more studies that quantify the β-cell lesion/mass and changes over time, particular with the newer agents in development, as this may indicate an effect of the intervention on the natural history of the disease. In the absence of hard outcomes, this may justify the effort to prevent diabetes. Finally, longitudinal studies of gastric bypass, which has profound effects on glucose metabolism, insulin sensitivity and β-cell function, would be helpful.

Conclusions

The evolving epidemic of diabetes represents a critical public health challenge in most developed and many developing countries. Patients with prediabetes can be easily identified with simple, widely available clinical measures. Such patients are at high risk for developing T2DM and CVD and should be targeted for intensive prevention efforts. Lifestyle interventions, emphasizing modest weight loss and increases in physical activity, are appropriate for most patients with prediabetes and are safe and effective. A number of trials have demonstrated that oral antidiabetic agents are effective at delaying onset of T2DM. TZDs are the most effective, but metformin, acarbose and orlistat are effective as well. In general, the natural history of progression to diabetes does not seem to be fundamentally altered with these interventions. If drug

therapy is contemplated, first consideration should be given to metformin which overall has a favorable safety, tolerability, efficacy and cost profile. This agent is especially useful in high-risk prediabetes subjects who are obese and under 60 years of age.

Conflict of interest

None declared.

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