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Strategies for preventing type 2 diabetes: an update for clinicians

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Abstract: Diabetes is a major and growing public health challenge which threatens to overwhelm medical services in the future. Type 2 diabetes confers significant morbidity and mortality, most notably with target organ damage to the eyes, kidneys, nerves and heart. The magnitude of cardiovascular risk associated with diabetes is best illustrated by its position as a coronary heart disease risk equivalent. Complications related to neuropathy are also vast, often working in concert with vascular abnormalities and resulting in serious clinical consequences such as foot ulceration. Increased understanding of the natural history of this disorder has generated the potential to intervene and halt pathological progression before overt disease ensues, after which point management becomes increasingly challenging. The concept of prediabetes as a formal diagnosis has begun to be translated from the research setting to clinical practice, but with continually updated guidelines, varied nomenclature, emerging pharmacotherapies and an ever-changing evidence base, clinicians may be left uncertain of best practice in identifying and managing patients at the prediabetic stage. This review aims to summarize the epidemiological data, new concepts in disease pathogenesis and guideline recommendations in addition to lifestyle, pharmacological and surgical therapies targeted at stopping progression of prediabetes to diabetes. While antidiabetic medications, with newer anti-obesity medications and interventional bariatric procedures have shown some promising benefits, diet and therapeutic lifestyle change remains the mainstay of management to improve the metabolic profile of individuals with glucose dysregulation. New risk stratification tools to identify at-risk individuals, coupled with unselected population level intervention hold promise in future practice.

Keywords: cardiometabolic, cardiovascular disease, diabetes, metabolic syndrome, obesity, preventive medicine, renin–angiotensin–aldosterone system (RAAS), vascular disease, weight loss

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Introduction

Individuals with type 2 diabetes mellitus (T2DM) have a unique propensity towards microvascular and macrovascular disease. Advances in preventive medicine have seen an effective reduction in the burden of risk from hypertension and hyperlipidaemia, but the incidence of diabetes has continued to rise, driving cardiovascular disease (CVD) rates [Gregg *et al.* 2005]. In 2011, there were 366 million people globally with diabetes, and the prevalence is estimated to reach 552 million by 2030, in part a consequence of the emerging epidemic in developing countries [International Diabetes Federation, 2012]. Even more alarming is the 280 million people with impaired glucose tolerance (IGT), and substantial numbers of undiagnosed diabetics. The healthcare expenditure is correspondingly vast.

Diabetes has been proposed as a coronary heart disease risk equivalent, which means diabetic patients without a history of coronary disease have an equivalent risk to that of nondiabetic individuals with confirmed heart disease [Haffner *et al.* 1998]. The consequences of diabetes are legion; diabetes represents the most common cause of end-stage renal disease [Molitch *et al.* 2004] and blindness in persons of working age [Evans, 1995] in the western world. The second edition of the Joint British Societies' guidelines [British Cardiac Society *et al.* 2005] and joint European guidelines [Ryden *et al.* 2007] made

empirical recommendations for blood pressure targets <130/80 mmHg in diabetic individuals, along with tight glycaemic control. However, a series of trials have recently questioned the benefit (and highlighted the potential risk) of intensive risk factor modulation in diabetes. ACCORD [Cushman *et al.* 2010] showed that intensive blood pressure control with combination therapy to achieve pressures of 119/64.4 mmHg did not provide any protection from the composite endpoint of nonfatal stroke or myocardial infarction compared with standard blood pressure control (133.5/70.5 mmHg) in individuals with T2DM. These findings were consistent with ADVANCE [Patel *et al.* 2007] and INVEST [Cooper-DeHoff *et al.* 2010], which did not support blood pressure lowering below 130 mmHg systolic.

Several studies have also failed to show any benefit in intensive glycaemic control on cardiovascular events or mortality [Hemmingsen *et al.* 2011]. The reasons for the increased mortality with very tight glycaemic control in ACCORD, and lack of benefit in ADVANCE and VADT are unclear but a number of potential explanations have been proposed [Rutter and Nesto, 2011]. Although there was a worse prognosis among intensively treated patients who experienced one or more episodes of severe hypoglycaemia, compared with those free of hypoglycaemic events, secondary analysis of all patients suffering hypoglycaemic events requiring assistance showed a nonsignificant trend to a lower risk of death in the intensive-treated group [Bonds *et al.* 2010]. Ultimately, only 1 out of 451 deaths in ACCORD were conclusively a consequence of hypoglycaemia, making it difficult to attribute this to the prognostic observations. There was an increased use of rosiglitazone in the intensive arm but no evidence to suggest this was responsible for the increased mortality either [Rutter and Nesto, 2011]. The increased weight gain in the intensively treated patients was substantial and, although not shown to be associated with mortality in the study, clearly remains noteworthy and potentially problematic for patients. In this respect, the more recent glucagon-like peptide-1 (GLP-1) agonists may provide valuable therapeutic options [Astrup *et al.* 2009]. Finally, given the reduction in myocardial infarction, it is possible that the follow up was insufficient to start seeing any mortality benefit.

Data from the UK Prospective Diabetes Study (UKPDS) did show a reduction in microvascular complications over 10 years of follow up, with differences in macrovascular disease apparent long term. Importantly, UKPDS involved more recently diagnosed patients, at an earlier course in their disease [UK Prospective Diabetes Study Group, 1998]. Even in newly diagnosed patients, microvascular disease is already present in up to a third due to asymptomatic hyperglycaemia prior to diagnosis [Kohner *et al.* 1998], shifting the focus of intervention upstream. The American Diabetes Association (ADA), the American Heart Association (AHA) and the American College of Cardiology (ACC) [Buse *et al.* 2007; Skyler *et al.* 2009; ADA, 2010] recommend HbA1c targets <7%, primarily because of microvascular benefits. ADA suggests a higher target would be acceptable in those with a longer history of diabetes, severe hypoglycaemia, poor prognosis or advanced cardiovascular or microvascular complications [ADA, 2010]. The National Institute of Clinical Excellence (NICE) in the UK emphasizes the importance of a patient-oriented and individualized target [NICE, 2008]. The most recent blood pressure guidelines from NICE have also taken recent trial data into consideration and do not recommend lowering blood pressure levels below 130/80mmHg as a general target [NICE, 2011]. For a comprehensive review of recent trials and guideline recommendation please see the review by Rutter and Nesto [Rutter and Nesto, 2011].

Prediabetes, obesity and metabolic syndrome

An increasingly overweight and obese population is the primary force driving the rising prevalence of diabetes. The Nurses' Health Study followed 84,941 females for up to 16 years, and reported a relative risk (RR) of diabetes of 38.8 and 20.2 for women with a body mass index (BMI) ≥35 and 30–34.9 kg/m^2 respectively, compared with women who had a BMI <23 kg/m^2. The influence of obesity and lifestyle on development of diabetes is further illustrated by migrating populations, such as the Pima Indians of Arizona, who have seen a dramatic increase in the prevalence of obesity and diabetes in concert with lifestyle changes from a traditional, active setting, to a westernized way of life [Knowler *et al.* 1978]. Over 21% of the English population are now classified as obese [Chaldakov *et al.* 2007] and the financial burden of obesity to health services is crippling, directly accounting for £2 billion of the National Health Service (NHS) budget. The latest global projections from the World Health Organization (WHO)

indicate that by 2015 approximately 2.3 billion adults will be overweight globally (BMI ≥25 kg/m^2) and over 700 million obese (BMI ≥30 kg/m^2) [World Health Organisation, 2009].

The Multiple Risk Factor Intervention Trial (MRFIT) shaped our current understanding of risk, shifting the focus away from arbitrary 'thresholds' and instead appreciating the continuous and graded relationship between risk factors and cardiovascular outcomes [Stamler *et al.* 1986]. Metabolic Syndrome (MetS) describes the cluster of risk factors, which predict and promote atherosclerotic CVD and T2DM. Different definitions exist depending on the institution and guidelines used, but all are based on combination of atherogenic dyslipidaemia, elevated blood pressure and dysglycaemia, in combination with excess body weight and obesity. The prime emphasis is on therapeutic lifestyle change to target obesity, sedentary lifestyle and atherogenic diet, which in turn have profound effects on lipid profile, hypertension and preventing diabetes (or controlling diabetes mellitus if present). The link between obesity, diabetes and CVD is multifactorial and involves complex interactions between adipokines and lipids, creating a pro-inflammatory microenvironment with the consequent endocrine and paracrine effects on the vasculature [Durrington, 2007]. For a detailed description please see the recent review by Romeo and colleagues [Romeo *et al.* 2012].

Although the pathogenesis of T2DM is complex, the central mechanism is impairment in the action of insulin (insulin resistance), combined with inadequate secretion of insulin itself. Investigators have proposed a multistage model of the development of T2DM [Weir and Bonner-Weir, 2004]. This follows an initial period of insulin resistance which is compensated for by increased insulin secretion from functional β-cells and increased β-cell mass, which work to maintain glycaemic levels. With chronic overactivity, there is a stage of stable adaptation, in which the β-cells are unable to fully compensate. This will initially manifest as IGT, characterized by postprandial hyperglycaemia and/or impaired fasting glucose (IFG), evidenced by mild fasting hyperglycaemia. High hepatic insulin resistance is typically seen in IFG, with almost normal values in skeletal muscle [Ferrannini *et al.* 2004; DeFronzo, 2009; DeFronzo and Abdul-Ghani, 2011], whilst in patients with IGT, the main site of insulin resistance is muscle, with only small changes in liver sensitivity [Abdul-Ghani *et al.* 2006; Ferrannini *et al.* 2011]. β-cell dysfunction is seen in both IFG and IGT. These two markers of defective glucose metabolism form the basis of the prediabetic state [Unwin *et al.* 2002; Cheng, 2005], although the clinical relevance of their mechanistic differences is uncertain. The following stage is decompensation with rapid rise in glucose levels [DeFronzo, 2009; Weir and Bonner-Weir, 2004]. This is illustrated by longitudinal studies [Sattar *et al.* 2007; Tabak *et al.* 2009; Mason *et al.* 2007], which show glucose values tightly regulated until 2–6 years before diagnosis, at which point there is a sharp increase.

In overweight adults up to 22.6% have been shown to have prediabetes [Benjamin *et al.* 2003], and approximately 5–10% of individuals with prediabetes will progress to diabetes in a year [Forouhi *et al.* 2007; Nathan *et al.* 2007]. Further, current estimates predict 472 million people having prediabetes worldwide by 2030 [Tabak *et al.* 2012]. There is significant discrepancy in rates of progression, with some population based observational studies reporting that 55–60% of individuals with IFG at baseline having normal fasting plasma glucose (FPG) at 10 years follow up [Nathan *et al.* 2007; Tabak *et al.* 2012]. This is dependent on the population studied, ethnicity, obesity and other cardiovascular risk factors present [Alberti, 1996]. Those individuals with dysglycaemia, combined with dyslipidaemia, hypertension and obesity appear to be most at risk of developing diabetes and subsequent CVD. Importantly, the risk also increases for those with higher prediabetic FPG values [Tirosh *et al.* 2005], leading to the proposal that these measures be regarded as continuous rather than discrete variables [Rathmann *et al.* 2010; Wilson *et al.* 2007], with the development of diabetes itself viewed as a continuous process [Tabak *et al.* 2012]. Of note, IFG is more prevalent in men than women [Cowie *et al.* 2009].

Some institutions have avoided the term 'prediabetes' to highlight the fact many individuals will not progress to diabetes. WHO has suggested 'intermediate hyperglycaemia', whilst an ADA commissioned panel preferred 'high risk state of developing diabetes' [International Expert Committee, 2009]. There is overlap between the various parameters of prediabetes [Tabak *et al.* 2012] and although the reproducibility of diagnostic criteria is lower than that for T2DM [Balion *et al.* 2007], the predictive value is higher than that of individual risk factors, with the combination of IFG and IGT more predictive than each parameter alone [Gerstein *et al.* 2007]. To date, no diabetes prediction tool has

Table 1. American Diabetes Association (ADA) and World Health Organisation (WHO) criteria for the diagnosis of prediabetes and diabetes mellitus. (Adapted from Ryden *et al*. [2007].)

Glucometabolic category	Guidelines	Classification criteria (mmol/l)
Impaired fasting glucose (IFG)	WHO	FPG ≥ 6.1 and < 7 + 2-h PG < 7.8
	ADA	FPG ≥ 5.6 and < 6.1
Impaired glucose tolerance (IGT)	WHO	FPG < 7 + 2-h PG ≥ 7.8 and < 11.1
	ADA	OGTT* 7.8–11
Impaired glucose homeostasis (IGH) and prediabetes	WHO	IFG or IGT
	ADA	IFG or IGT or HbA1c 5.7–6.4%
Diabetes mellitus	WHO	FPG ≥ 7 or 2-h PG ≥ 11.1
	ADA	FPG ≥ 7 or OGTT ≥ 11.1 or HbA1c ≥ 6.5% or random blood glucose ≥ 11.1 with classical symptoms

*OGTT is performed in the morning after 8–14 h fast: one sample is taken before and one 120 min after intake of 75 g glucose dissolved in 250–300 ml water for 5 minutes.
2-h PG, 2-hour post-load plasma glucose; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

been universally accepted, but it is likely the most effective model will consist of an initial 'prescreen' based on routine clinical values, following by a more detailed assessment for certain at-risk individuals (e.g. overweight) with laboratory measures [Tabak *et al.* 2012; Buijsse *et al.* 2011] (Table 1).

Fasting hyperglycaemia, post-load glucose and HbA1c have been shown in multivariable adjusted analyses to be predictive of vascular mortality independent of vascular risk factors such as obesity, blood pressure and lipid profile [Emerging Risk Factors Collaboration *et al.* 2011; Tabak *et al.* 2012]. As well as predicting the development of diabetes, prediabetes itself is associated with increased risk of disease [Liao *et al.* 2001]. Epidemiological studies, such as the Australian Diabetes and Lifestyle (AusDiab) project, have shown clearly that target organ damage precedes the diagnosis of T2DM, with both renal [Tapp *et al.* 2004] and retinal [Tapp *et al.* 2003] damage seen in patients with IGT. A number of other population studies have confirmed that individuals with IFG [Shaw *et al.* 1999] and IGT [Tominaga *et al.* 1999] have increased risk of developing macrovascular disease; around a third of patients with coronary artery disease (CAD) have abnormal oral glucose tolerance test (OGTT), and 22% with acute and 14% with stable coronary heart disease have newly diagnosed T2DM.

There is a particularly strong association between prediabetes and autonomic neuropathy, with consistent reports of disordered parasympathetic function [Tesfaye *et al.* 2010; Wu *et al.* 2007; Putz *et al.* 2009] and sensory neuropathy [Hoffman-Snyder *et al.* 2006; Singleton *et al.* 2001]. Diabetic autonomic neuropathy can affect a number of organ systems, with cardiovascular symptoms including resting tachycardia, orthostatic hypotension and silent myocardial ischaemia, and cardiovascular autonomic neuropathy is significantly associated with overall mortality [Vinik and Ziegler, 2007]. Diabetes is also the most common cause of chronic peripheral neuropathy; chronic hyperglycaemia with associated metabolic abnormalities, redox imbalance, dyslipidaemia and advanced glycation end products (in conjunction with microvascular disease) are some of the multifactorial insults contributing to nerve pathology in diabetes [Tesfaye *et al.* 2010]. Pain and autonomic symptoms are typical. Therapies to treat diabetic neuropathy are still being actively pursued and range from aldose reductase inhibitors [Hotta *et al.* 2008] to antioxidants [Ametov *et al.* 2003] and angiotensin-converting enzyme (ACE) inhibitors [Malik *et al.* 1998]. Patients with idiopathic small fibre neuropathy and diabetes or IGT have been shown to exhibit corneal changes, which can be detected and quantified by corneal confocal microscopy. This potentially powerful diagnostic tool may provide the earliest and most sensitive test to detect small fibre damage in diabetes and prediabetes. Importantly, the corneal changes appear to be graded with severity of disease, permitting quantification and monitoring of therapeutic interventions. For a comprehensive discussion of the topic please refer to the review by Tavakoli and colleagues [Tavakoli *et al.* 2012].

Updated versions of the Joint British Societies' guidelines [British Cardiac Society *et al.* 2005] and joint European guidelines [Graham *et al.* 2007] are awaited, but the latest available documents recommend optimal fasting plasma glucose (FPG) ≤6 mmol/l in high-risk individuals. If the FPG reading is ≥6.1, fasting glucose measurements are advised to look for IFG or new diabetes mellitus (DM). If this is 6.1–6.9 mmol/l, a repeat sample on a separate occasion, or an OGTT is advised, and a second abnormal value confirms IFG. If ≥7 mmol/l with symptoms (polyuria, polydipsia, weight loss), DM is diagnosed, otherwise two separate readings are needed. An OGTT is the only way to diagnose IGT (2-hour glucose ≥7.8 but <11.1 mmol/l) and is the conventional standard for the diagnosis of DM (2-hour glucose ≥11.1 mmol/l). ADA recommends screening for diabetes in asymptomatic individuals ≥45 years of age, or in those with BMI ≥25 and one additional risk factor for DM. Appropriate tests include HbA1c, FPG or 2-hour 75 g OGTT. The European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) guidelines did not make specific recommendations regarding screening. Both Diabetes UK and WHO support the use of HbA1c in diagnosing diabetes. Individuals with prediabetes should undergo intensive therapeutic lifestyle change, with appropriate follow up, counselling and support, with annual reviews to monitor for progression to DM. Modulating cardiovascular risk in diabetes is clearly a challenging task. We have already discussed the failure of very tight glycaemic and blood pressure control in preventing hard cardiovascular endpoints. This was highlighted in a recent meta-analysis [Hopper *et al.* 2011], which was unable to identify any effective pharmacological strategy to prevent cardiovascular mortality in prediabetes, even when therapies were successful in preventing overt diabetes.

Nonpharmacological intervention

Weight loss improves outcomes in T2DM and delays or prevents progression from IGT/IFG to diabetes. Epidemiological data from the Framingham Study [Moore *et al.* 2000] has shown that sustained weight loss in overweight individuals can have a primary preventative effect on the incidence of T2DM, with a moderate weight loss of approximately 4 kg protective against progression to T2DM in at-risk patients [Van Gaal, 2005]. Consequently, many strategies aimed at preventing T2DM have focused primarily on weight loss, which has made it difficult to determine the independent effects of weight loss, dietary changes and exercise due to their combination in a lifestyle intervention arm of many studies. The largest study to date was conducted by the Diabetes Prevention Program (DPP) research group [Knowler *et al.* 2002]. This involved 3234 nondiabetic (ethnically and racially diverse) individuals with IGT of mean age 51 years and BMI 34 kg/m^2 randomized to placebo, metformin or lifestyle intervention. The lifestyle intervention group were expected to maintain a weight reduction of 7% through dietary means and physical activity, performing at least 150 minutes of moderate intensity activity per week. Lifestyle intervention was associated with an impressive 58% reduction in the incidence of diabetes compared with placebo and superior to metformin. Indeed, for every 1 kg reduction in weight there was an associated 16% reduction in incidence of diabetes. Follow-up studies have confirmed that this preventative or delaying effect persists at 10 years [Knowler *et al.* 2009]. *Post hoc* analysis [Ratner *et al.* 2008] also confirmed the extreme propensity of gestational diabetes mellitus (GDM) on progression to diabetes, with a 71% higher incidence than those without a history of GDM (despite similar glucose levels at entry). Women with GDM randomized to metformin benefited from a 50% reduction in incidence of diabetes, compared with 14% in those without GDM.

The Finnish Diabetes Prevention Study (FDPS) [Tuomilehto *et al.* 2001] examined the benefits of lifestyle on preventing diabetes in 522 middle-aged, overweight (BMI ≥25 kg/m^2) subjects with IGT. Subjects in the intervention group were counselled to achieve a reduction in weight of at least 5% through a tailored exercise programme consisting of 30 minutes of moderate exercise each day, 30% reduced calorie intake, reduced dietary fat and increased dietary fibre. A mean weight loss of 3.5 kg was observed after 3.2 years in the intervention group, compared with 0.8 kg in the control group. The intervention group had a 58% RR reduction in the incidence of T2DM, remarkably with no incidence of diabetes in those individuals successful in achieving 80% of their diet, exercise and lifestyle goals. The Chinese Da Qing IGT and Diabetes Study [Pan *et al.* 1997] compared diet, exercise, and diet with exercise, *versus* placebo in 577 subjects with IGT. After 6 years of follow up, a 31, 46 and 42% reduction in risk of developing diabetes was observed in the diet only, exercise

only and combined intervention groups, respectively. The Indian Diabetes Prevention Programme found HbA1c as the most powerful predictor of incident diabetes [Ramachandran *et al.* 2012] among Asian Indian subjects with IGT. Although there are ethnic variations in HbA1c, recent ADA guidelines have now included HbA1c as a parameter to define prediabetes. A recent randomized study of overweight Japanese subjects with IFG levels at initial screening [Saito *et al.* 2011] demonstrated that lifestyle interventions in participants with both IFG and IGT were remarkably effective, but not in those with isolated IFG, suggesting IGT may represents a better target for lifestyle interventions than IFG.

Translating these findings from clinical trials to a clinical setting has been challenging. An ADA statement on prevention of T2DM [Sherwin *et al.* 2004] acknowledges the difficulty in replicating the lifestyle interventions from the DPP [Knowler *et al.* 2002] and FDPS [Tuomilehto *et al.* 2001], which require considerable effort, resources and funding. Sustaining any changes is an additional challenge to the individual and health services. The recent Diabetes UK Nutrition Working Group emphasized the need to raise awareness of the risks of unhealthy lifestyles to help patients with diabetes to achieve effective self-management [Dyson *et al.* 2011]. Disappointingly, 20-year results from the Chinese Da Qing IGT and Diabetes Study [Li *et al.* 2008] and 10-year results from the FDPS [Uusitupa *et al.* 2009; Ilanne-Parikka *et al.* 2008] have failed to demonstrate significant benefits of lifestyle intervention on CVD morbidity or mortality, despite sustained reduction in the incidence of diabetes after discontinuation of intervention. This was corroborated by a recent meta-analysis of 10 prospective randomized controlled trials [Hopper *et al.* 2011], including a total of 23,152 individuals with prediabetes, which demonstrated no difference in all-cause mortality or cardiovascular death from interventions to prevent diabetes (of which lifestyle measures were superior to pharmacotherapy), despite their efficacy in preventing diabetes. The lack of benefit in these hard endpoints is surprising and the reasons unclear.

Pharmacological intervention

Anti-obesity medication

Given the intertwined relationship between obesity and diabetes, one can extrapolate the likely metabolic benefits from clinical trials of weight loss medications, whilst some appropriately designed studies have specifically examined glycaemic endpoints. These are discussed below. What becomes apparent is that, although a number of drugs have emerged as promising weight loss medications, some initially approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA), postmarketing surveillance has unfortunately identified significant adverse effects with many of these agents now withdrawn.

Sibutramine. Sibutramine was released as a safer alternative to fenfluramine–phentermine, or 'fenphen' (a serotonin, norepinephrine and dopamine releasing agent) and dexfenfluramine (the *d*-enantiomer of fenfluramine), which were withdrawn due to potentially fatal adverse effects such as pulmonary hypertension and valvular heart disease [Dahl *et al.* 2008]. Sibutramine also works through inhibiting serotonin and norepinephrine re-uptake, resulting in enhanced satiety, reduced calorie intake and therefore weight loss. The STORM study [James *et al.* 2000] (Sibutramine Trial of Obesity Reduction and Maintenance) showed that combined intervention with sibutramine and comprehensive lifestyle management achieved weight loss of 5% body weight in over three-quarters of participants within 6 months. In those who achieved weight loss, further randomization confirmed rapid weight gain over 18 months following discontinuation of treatment, whilst continued use of sibutramine maintained weight loss almost entirely during the follow-up period. A meta-analysis of 8 placebo-controlled double-blind randomized trials of sibutramine [Vettor *et al.* 2005], involving a total of 1093 obese patients with T2DM reported a 5.5 kg average weight loss in those treated with sibutramine group, with significant reductions in HbA1c of 0.28% and small but significant reductions in basal blood glucose levels. Sibutramine was, however, associated with increased systolic and diastolic blood pressure and heart rate, in addition to prolongation of the QT interval [Rubio *et al.* 2007]. The Sibutramine Cardiovascular OUtcome Trial (SCOUT) assessed CVD outcomes in 10,744 patients and confirmed an increase in CVD events of 16% ($p = 0.02$), leading to withdrawal of the drug [James *et al.* 2010].

Orlistat. Orlistat is a gastrointestinal lipase inhibitor that interferes with fat absorption in the gut and has shown greater promise. The XENDOS

study examined the effect of orlistat as an adjunct to an intensive lifestyle programme (consisting of a strict diet and exercise regime) in a double-blind randomized controlled trial of 3,305 obese non-diabetic subjects, 21% of whom had IGT at baseline. The addition of orlistat was associated with a significant increase in weight reduction compared with lifestyle alone, with weight reductions of 5.8 kg and 3 kg respectively, over 4 years of follow up. The orlistat group was associated with a 37% RR reduction in the incidence of diabetes compared with those receiving placebo. These glycaemic benefits exceeded that attributable to weight loss alone [Rubio *et al.* 2007]. Direct benefits on insulin sensitivity [Kelley *et al.* 2004] are a proposed mechanism, with release of protective hormones such as incretin and glucagon-like peptide 1 secondary to improved lipid profiles [Damci *et al.* 2004]. Orlistat has also been reported to have favourable effects on leptin, resistin and adiponectin levels [Rucker *et al.* 2007]. It should be noted XENDOS suffered a very high dropout rate, with only a 52% completion rate in the orlistat group and 34% in the placebo group. The X-PERT study further supported these findings. Treatment with a combination of orlistat and lifestyle intervention resulted in greater weight loss than lifestyle alone, with improved metabolic parameters [Toplak *et al.* 2005]. A meta-analysis of 5 double-blind randomized placebo controlled trials [Rucker *et al.* 2007], involving 1678 participants revealed a weighted mean difference of −1.03 mmol/l in fasting glucose and -0.38% in HbA1c for individuals treated with orlistat compared with placebo. The most common side effects of orlistat are gastrointestinal, including increased defecation, fatty stools, leaking of oil from the rectum, faecal urgency and incontinence. Orlistat can also decrease fat-soluble vitamin absorption but not beyond the reference range [Rubio *et al.* 2007].

Rimonabant. The endocannabinoid system is central to energy homeostasis. There are two cannabinoid receptor subtypes: CB1 and CB2. The CB1 receptor is ubiquitously expressed in the brain and peripheral tissues, whilst the CB2 receptor is found in the immune system and does not appear to be involved in energy metabolism [Di Marzo and Matias, 2005]. The endocannabinoid system is overexpressed in obese subjects [Engeli *et al.* 2005] and mechanistic studies in animals have shown alterations in food intake with administration of cannabinoid agonists/ antagonists [Ligresti *et al.* 2009]. Rimonabant is a selective CB1 receptor blocker and the Rimonabant-in-Obesity (RIO) programme has examined the metabolic effects of rimonabant through a number of different studies. RIO-Europe [Van Gaal *et al.* 2005] enrolled subjects with BMI >30 or >27 kg/m^2 with either hypertension or dyslipidaemia. At 1 year, 67% of those who completed the trial achieved a 5% weight loss and almost half achieved a weight loss of 10%. This was associated with significant improvement in glycaemic levels. The RIO-lipid study [Despres *et al.* 2005] was performed in 1036 obese or overweight individuals with untreated dyslipidaemia and demonstrated improvements in lipid profile, increased adiponectin levels, and reduction in MetS from 52.9% at the start to 25.8% after 1 year of treatment. The RIO-Diabetes study [Scheen *et al.* 2006] investigated the efficacy of rimonabant in 1047 overweight and obese individuals with T2DM who were previously on monotherapy with metformin or sulfonylurea. After 1 year of treatment, the rimonabant treated group experienced an average weight loss of 5.3 kg *versus* 1.4 kg in the placebo group. Those individuals treated with rimonabant benefited from a 0.6% reduction in HbA1c levels, from a mean of 7.3% at baseline. Furthermore, 43% of individuals treated with rimonabant achieved optimal HbA1c levels compared with 21% of those given placebo. Other cardiometabolic risk factors such as waist circumference, high-density lipoprotein (HDL), cholesterol, triglycerides, insulin resistance, systolic blood pressure and C-reactive protein (CRP) were also improved significantly.

The 6-month Study Evaluating Rimonabant Efficacy in Drug-NAive DiabEtic Patients (SERENADE) trial [Rosenstock *et al.* 2008] confirmed that, in individuals recently diagnosed with T2DM yet to commence medication, treatment with rimonabant was associated with 0.8% reduction in HbA1c. RIO-North America [Pi-Sunyer *et al.* 2006] enrolled 3405 obese patients and confirmed that subjects who continued treatment lost an average of 7.4 kg, with declining levels of MetS, whereas those re-randomized to placebo gained much of their weight. Effects at 1 year on fasting insulin and Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) were approximately twice that attributable to concomitant weight loss. The most common adverse effects of rimonabant were mild nausea and diarrhoea. However, depressed mood, anxiety, agitation, suicidal ideation and sleep disorders were noted as serious adverse events in cases of drug withdrawal [Akbas *et al.* 2009]. The Comprehensive Rimonabant Evaluation Study of Cardiovascular

ENDpoints and Outcomes (CRESCENDO) trial of individuals with or at high risk of CVD was terminated early due to excess suicides in the rimonabant arm after 18 months [Topol *et al.* 2010]. Subsequently rimonabant was withdrawn from the market in US and Europe 2008 [Taylor, 2009]. Experiments with rimonabant derivatives in animal models suggest that peripheral CB1 antagonists may lack the anxiogenic actions of the parent compound while retaining its metabolic benefits [Tam *et al.* 2010].

A number of other weight loss medications have been tested [Rutter and Nesto, 2011], such as combinations of low dose naltrexone and bupropion in the COR-I trial [Greenway *et al.* 2010], phentermine and topiramate in CONQUER [Gadde *et al.* 2011] and the 5-hydroxytryptamine-3c (5HT-3c) antagonist lorcaserin in the BLOOM trial [Smith *et al.* 2010]. Although these did show some benefit in weight loss, the effects were small and insufficient to permit their licensing.

Targeting gut hormones. Gut hormones have emerged as useful targets against diabetes and obesity. Peptide tyrosine tyrosine (PYY_{3-36}) and GLP-1 are hormones released by the L-cell of the distal ileum which reduce food intake [Batterham *et al.* 2002; Chelikani *et al.* 2005a, 2005b] and cause significant weight loss [Chelikani *et al.* 2006]. GLP-1 is rapidly degraded by dipeptidyl peptidase-IV (DPP-IV) and only has a half-life of 2 minutes [Deacon *et al.* 1995]. PYY_{3-36} has a half-life of 9 min, perhaps due to cleavage from neutral endopeptidase [Medeiros and Turner, 1994]. GLP-1 analogues are approved for the treatment of T2DM. Exenatide and liraglutide have an acyl chain bound to the amino terminus and are therefore resistant to DPP-IV [Knudsen *et al.* 2000]. Early trials of GLP-1 analogues showed small reductions (2–3 kg) or no effect on weight. The Liraglutide Effect and Action in Diabetes (LEAD) trials consisted of 5 studies of 26–52 weeks duration, including more than 3900 patients, and investigated the effect of liraglutide on weight-related endpoints. Results from trials showed that, as a single agent and in combination with other antidiabetic medications, these drugs significantly reduced HbA1c ranging, in monotherapy, from 1.0 to 1.5% in patients with baselines HbA1c 8.2 to 8.6%, and HbA1c by 1.0% in combination with metformin. The 1.8 mg dose of liraglutide was associated with a further reduction in weight of 2 kg despite lack of additional efficacy in reducing HbA1c in a trial of 564 obese patients with diabetes [Astrup *et al.* 2009]. Common adverse reactions of GLP-1 analogues include headache, nausea, diarrhoea and specific antibody formation. Immunogenicity-related events, such as urticaria, were also reported. FDA and EMA are looking to ascertain additional information on the safety of GLP-1 analogues and several post-marketing studies are planned, although the current consensus is that these therapies provide a very effective option for overweight diabetic individuals. Longer lasting PYY preparations have also been developed. A PEGylated PYY molecule has been shown to have a dramatically longer half-life and to inhibit food intake for a longer period than native PYY, and to also cause significantly greater weight loss in a chronic setting compared with PYY in experimental animals [Ortiz *et al.* 2007]. A multicentre multinational study investigated the effect of nateglinide (a short-acting insulin secretagogue) in more than 9000 people with IGT and reported no effect on the rate of diabetes or cardiovascular outcomes during 6.5 years of follow up [Holman *et al.* 2010; Tabak *et al.* 2012].

Oral diabetic agents

Metformin. Metformin is of the biguanide class of drugs, and works predominantly through reducing hepatic glucose output [Nathan *et al.* 2009; Tabak *et al.* 2012]. Clinical trials have consistently shown the benefit of metformin in preventing T2DM, although to varying degrees depending on the dose, adjunct lifestyle modifications, and particularly the body weight of the cohort examined. The most convincing evidence came from the DPP, which has already been discussed in relation to outcome findings for the lifestyle intervention arm [Knowler *et al.* 2002]. Following a mean follow up of 2.8 years, the incidence of new onset diabetes was 4.8% in the metformin-treated cohort compared with 7.8% in the placebo group; demonstrating a RR of 0.69 [number needed to treat (NNT) of 14 over 3 years to prevent 1 new case of T2DM]. There was an average 2.1 kg weight loss of individuals in the metformin group and those subjects most likely to benefit were those with BMIs >35 kg/m^2 at baseline, in whom it reduced the incidence of diabetes by approximately 50% [Walker *et al.* 2006]. Importantly, this effect remained significant after a 1–2-week washout period, with an overall RR of 0.7 in favour of genuine disease prevention rather than acute glucose lowering.

The Chinese Diabetes Prevention Study (CDPS) [Yang *et al.* 2001] was a smaller trial involving a much leaner cohort (mean BMI 25) of 321 middle-aged patients and IGT as determined from a single OGTT. Participants were divided into three groups: those receiving education alone, metformin or acarbose. During a 3-year follow-up period, there was a 76.8% reduction in progression to diabetes in the metformin group compared with controls, but an 88% reduction in the acarbose group. There was a small, nonsignificant reduction in BMI in both groups. These findings are in contrast to the Early Diabetes Intervention Trial (EDIT) [Holman *et al.* 2003], which was a double-blind, placebo-controlled trial of 631 participants with 2 consecutive IFG readings that failed to demonstrate any benefit in the delay of onset or prevention of diabetes with acarbose, metformin or combination therapy over a 6-year follow-up period. The Indian Diabetes Prevention Programme (IDPP-1) [Ramachandran *et al.* 2006] showed that metformin and lifestyle modifications were associated with relative reductions in the incidence of diabetes of 26.4% and 28.5% respectively, whilst the combination of the two was associated with no greater benefit. There was no associated weight loss in the metformin group, although the dose of metformin was lower in this trial (average of 250 mg twice daily) compared with others.

A recent meta-analysis looked at the effect of metformin on a number of cardiometabolic parameters in nondiabetic individuals, as well as the incidence of new onset diabetes [Salpeter *et al.* 2008]. The analysis consisted of 31 randomized trials carried out between 1996 and 2006, with a minimum of 8 weeks duration and a total of 4570 individuals followed up for 8267 patient years. Metformin was shown to reduce BMI, insulin resistance, triglycerides and low density lipoprotein (LDL) cholesterol, and had an overall reduction in the incidence of new-onset diabetes by 40% [confidence interval (CI) 0.5–0.8) and an absolute risk reduction of 6% (CI 4–8) during a mean trial duration of 1.8 years. A smaller meta-analysis of three trials with IGT showed similar findings, with a 45% reduced risk of T2DM [Lily and Godwin, 2009; Tabak *et al.* 2012].

Sulphonylureas and glinides. Few studies have examined the effect of insulin-secreting antidiabetic agents on development of new onset T2DM. The UKPDS showed transient improvements in glycaemic control, but with a rebound increase in HbA1c after several years. More recently, A Diabetes Outcome Progression Trial (ADOPT) [Kahn *et al.* 2006], showed a lower failure rate (time to monotherapy failure, defined by a FPG >180 mg/dl) at 5 years of 15% with rosiglitazone *versus* 21% with metformin and 34% with glyburide. Several studies have reported that tolbutamide has no proven benefit on prevention of diabetes in cohorts with IGT or IFG compared with placebo [Keen *et al.* 1973; Sartor *et al.* 1980; Herlihy *et al.* 2000]. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) [Califf *et al.* 2008] recruited 9306 individuals with IGT and established or at high risk of CVD, and compared the effects of placebo with nateglinide and valsartan in combination or in isolation. There was a 6% nonsignificant decrease in the primary endpoint of new diabetes, and a 7% nonsignificant reduction in CVD events with nateglinide, although this was associated with increased hypoglycaemic events [Holman *et al.* 2010].

Thiazolidinediones. Thiazolidinediones, or the 'glitazones', work through the peroxisome proliferators activated receptor-γ, increasing insulin sensitivity in both the liver and peripheral tissues, therefore decreasing glucose load on β-cells. In TRoglitazone In the Prevention Of Diabetes (TRIPOD) [Buchanan *et al.* 2002] study, a subgroup of the DPP trial, 236 Hispanic women with prior gestational diabetes (70% of whom had IGT) were randomized to troglitazone or placebo (mean age of 34.6 years, BMI 30.5 kg/m^2). Troglitazone reduced the risk of developing diabetes by approximately 55% over 2.5 years, but the drug was removed from the market due to hepatic toxicity. Prior to its premature discontinuation from the DPP [Knowler *et al.* 2005], troglitazone reduced the incidence of diabetes by 75% in the 585 subjects in whom it was tested over a 0.9-year follow up.

The newer class of glitazones, rosiglitazone, has been studied in 5269 patients with IFG, IGT or both over a 3-year period in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial [Gerstein *et al.* 2006]. The incidence of diabetes was reduced by 62% and furthermore 50% of rosiglitazone-treated patients reverted to normoglycaemia (compared with 30% in the placebo group). Rosiglitazone appeared most effective in individuals with a high BMI. Data from Act Now for Prevention of Diabetes (ACT-NOW) showed

a 78% reduction in the conversion of IGT to T2DM with pioglitazone [DeFronzo *et al.* 2011]. Unfortunately, due to reported side effects including weight gain, increased rates of congestive heart failure, osteoporotic fractures and CVD events with rosiglitazone (but not pioglitazone), the potential of these glitazones has been limited. Rosiglitazone has now been withdrawn in Europe and pioglitazone from Germany and France.

α-Glucosidase inhibitors. The α-glucosidase inhibitors reduce the rate of polysaccharide digestion from the proximal small intestine and reduce postprandial glucose. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial [Chiasson *et al.* 2002] reported that acarbose, an inhibitor of α-glucosidase, was associated with a 25% reduction (based on a single OGTT) in the incidence of diabetes over a follow-up period of 3.3 years in a large cohort of 1368 high-risk individuals with IGT, a mean age of 54.5 years and BMI of 31. Efficacy of acarbose was independent of age, sex or BMI. It should be noted, however, that approximately a quarter of study participants withdrew from the study due to the well-recognized gastrointestinal side effects associated with acarbose. If the study had adopted a diagnosis based on two positive OGTT readings, as recommended by ADA [Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997], acarbose would have been associated with a 36.4% reduction in the incidence of diabetes. In addition, this study provided evidence to support reduced CVD and hypertension risk in treated IGT patients. After acarbose treatment and reversion of IGT, treatment with placebo for 3 months has been shown to increase conversion of IGT to diabetes, perhaps due to a masking effect [Scheen, 2009]. Another α-glucosidase inhibitor, voglibose, was recently shown to reduce the risk of progression to T2DM by 40.5% in a cohort of Japanese patients with IGT [Kawamori *et al.* 2009]. Furthermore, in comparison with placebo, treatment with voglibose was associated with a 53.9% increase in successful achievement of normoglycaemia.

Other pharmacological interventions

Renin–angiotensin blockade. *Post hoc* analysis of CVD and blood pressure lowering trials have provided some evidence in support of the protective effects of renin–angiotensin blockade against developing diabetes. The Heart Outcome Protection Evaluation (HOPE) [Yusuf *et al.* 2000] showed that patients treated with the angiotensin converting enzyme inhibitor (ACE-I) ramipril benefited from a 34% relative reduction in the incidence of newly diagnosed diabetes compared with placebo. The Captopril Prevention Project (CAPPP) [Scheen, 1999] demonstrated a RR reduction of 14% in the incidence of diabetes in those individuals receiving captopril compared with those on conventional antihypertensive treatment with diuretics and/or beta-blockers. The Antihypertensive Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [ALLHAT Collaborative Research Group, 2000] compared chlorthalidone with lisinopril, doxazosin and amlodipine as initial first-choice blood pressure lowering agents, demonstrating a RR reduction in developing diabetes of 30% associated with ACE blockade. Losartan Intervention for End Point Reduction in Hypertension(LIFE) [Lindholm *et al.* 2002] and Valsartan Antihypertensive Long-term Use Evaluation (VALUE) [Kjeldsen *et al.* 2006] compared the effects of angiotensin-II receptor blockers (ARBs) with beta-blockers and calcium antagonists, respectively. Both studies showed benefits in the range of 23–25% reductions in the incidence of diabetes in favour of angiotensin blockade. The Study on Cognition and Prognosis in the Elderly (SCOPE) [Lithell *et al.* 2003] compared candesartan cilexetil and placebo and corroborated these findings, with a RR reduction of 25%. The mechanism of this protection is thought to be related to vasodilatation affording increased muscular and pancreatic blood flow [Scheen, 2004b], with beneficial redox effects on insulin signalling [Leiter and Lewanczuk, 2005], adipocytes recruitment, and peroxisome proliferation [Scheen, 2004b]. These trials were not designed to examine diabetic endpoints, making it difficult to draw firm conclusions from these data, especially given that diuretics and beta-blockers were frequent in comparison arms (with the exception of HOPE and VALUE [Braga and Leiter, 2009]), which reduce insulin sensitivity and may amplify any apparent benefits from renin–angiotensin blockade.

A large meta-analyses of 22 trials [Elliott and Meyer, 2007] and over 143,000 patients, mostly with hypertension, demonstrated a RR reduction of 0.57 (CI 0.46–0.72) and 0.67 (CI 0.56–0.80) in the incidence of diabetes in patients treated with ARBs and ACE-Is, respectively, when compared with treatment with diuretics. A second meta-analysis [Scheen, 2004a] of 10 studies and 76,000 patients showed a 22% reduction in the

incidence of diabetes with renin–angiotensin blockade in patients with hypertension and heart failure. However, in the setting of a well-designed randomized controlled trial, ACE-Is were not shown to reduce the incidence of diabetes: Diabetes Reduction Approaches With Ramipril and Rosiglitazone Medications (DREAM) [Bosch *et al.* 2006] recruited 5269 patients with IFG or IGT but without known CVD, and randomized them to receive ramipril or placebo, as well as rosiglitazone or placebo. Interestingly, ramipril did not reduce the primary endpoint of new onset diabetes or death after 3 years of follow up but did significantly increase regression to normoglycaemia. The young average age of the cohort, length of follow up and small population size may explain the negative findings. The NAVIGATOR trial recruited 9306 individuals with IGT and established or at high risk of CVD, and compared the effects of placebo with nateglinide and valsartan in combination or in isolation. Primary endpoints were the onset of new diabetes as well as CVD endpoints. In the NAVIGATOR trial, valsartan therapy reduced new diabetes by 14% ($p < 0.001$) but had no effect on CVD events [Holman *et al.* 2010].

Statins. *Post hoc* analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) [Freeman *et al.* 2001] assessed the effect of pravastatin on development of diabetes. After 4.8 years mean follow up, pravastatin was associated with a 30% reduction in the development of new onset diabetes based on fasting blood glucose [hazard ratio (HR) = 0.7; 95% CI 0.5–0.98]. In contrast, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [Ridker *et al.* 2008] in 17,802 primary prevention patients at moderate CVD risk, rosuvastatin 20 mg therapy was associated with an increase in physician-reported new diabetes (270 *versus* 216 cases; $p = 0.01$) and a 0.1% increase in HbA1c. A later meta-analysis showed that statin therapy in general was associated with hyperglycaemia and a 9% increase in new onset diabetes [Sattar *et al.* 2010]. The mechanism by which statins may increase the incident risk of diabetes is unclear, however, a number of possible theories have been suggested [Sattar and Taskinen, 2012], based around inflammatory and oxidative mechanisms which alter islet β-cell insulin secretion causing impaired glucose metabolism [Sampson *et al.* 2011]. There is also evidence for risk genotypes predisposing to β-cell dysfunction with statins [Stancakova *et al.* 2009].

Surgical intervention

Bariatric surgery achieves weight loss by restrictive or malabsorptive mechanisms. The *Roux-en-Y* gastric bypass, a combination of the two, is associated with the best outcomes and is therefore accepted as the criterion standard [Buchwald *et al.* 2004]. Bariatric surgery is currently offered to morbidly obese patients (BMI >40 kg/m^2) and obese patients (BMI ≥35 kg/m^2) with significant comorbidities that may be ameliorated by weight loss. Its inclusion criteria are, however, likely to broaden as a result of accumulating evidence suggesting bariatric surgery confers improvement in metabolic and cardiovascular risk [Wierzbicki, *et al.* 2011]. Long-term outcomes in patients undergoing obesity surgery have confirmed a reduction in overall mortality compared with conventional treatment for obesity [Sjostrom *et al.* 2007]. Evidence suggests that bariatric surgery can induce long-term remission of T2DM in both obese and morbidly obese patients. One meta-analysis of over 600 studies reported resolution of diabetes in 78% of patients following bariatric surgery, verified by serum insulin, HbA_{1c} and fasting blood glucose levels [Buchwald *et al.* 2009].

The Swedish Obese Subjects (SOS) study [Sjostrom *et al.* 2004], a prospective, nonrandomized trial comparing bariatric surgery with conventional nonsurgical treatment, included 4047 patients with a BMI ≥34 for men or BMI ≥38 for women. Patients who underwent bariatric surgery had greater rates of remission from diabetes and lower 2- and 10-year incidence rates of diabetes (1 and 7%, respectively) compared with a control group receiving conventional therapy (8 and 24%, respectively). Interestingly, the risk of developing diabetes reduced in parallel to the amount of weight loss. At 2 and 10 years follow up, weight increased by 0.1 and 1.6% respectively in the conventional treatment group, in contrast to weight reductions of 23.4 and 16.1% at the same follow-up periods in the bariatric surgery group. Bariatric surgery was associated with reduced overall mortality, although there was insufficient power to confirm that the survival benefit was attributable to weight loss.

Evidence suggests that bariatric surgery may result in improvements in hyperlipidaemia and hypertension in as many as 70% and 78.5% of patients respectively [Buchwald *et al.* 2004]. Such modification of cardiovascular risk may, in part, explain a concomitant reduction in CAD mortality rates

[Adams *et al.* 2007]. The mechanisms behind the prevention and remission of T2DM following bariatric surgery remain unclear, however, evidence suggests it exerts a broader physiological role than weight loss alone. Alterations in metabolism including improvements in glycaemic control have been shown to take place before any significant weight loss is achieved [Pories *et al.* 1995], and bypassing the proximal small intestine in lean diabetic rats ameliorates T2DM independent of effects on body weight [Rubino *et al.* 2006]. Neuroendocrine mechanisms are likely to play a key role in weight loss independent improvements in glucose tolerance and insulinaemia. Bariatric surgery reduces levels of ghrelin (appetite stimulator) and increases postprandial PYY responses (mediate appetite inhibition) and insulin secretion due to increased incretin and GLP-1 levels [Le Roux *et al.* 2006; Rubino *et al.* 2004].

Despite limited evidence regarding the efficacy of bariatric surgery in patients who are not morbidly obese, recent data may further the argument that the inclusion criteria should be expanded. Data from two case series [Chiellini *et al.* 2009; Arguelles Sarmiento, 2005] and one randomized controlled trial (RCT) [Dixon *et al.* 2008] involving diabetic patients with a BMI <35 have reported promising results, but the small number of patients involved provide insufficient evidence to update the arbitrary BMI cutoffs endorsed by the 1991 National Institute of Health Consensus Conference Guidelines [Consensus Development Conference Panel, 1991]. As highlighted in the recent Diabetes Surgery Summit (DSS), the identification of appropriate criteria for patient selection in patients with a BMI <35 should be considered a priority for forthcoming clinical trials. [Rubino *et al*. 2010]

Conclusions

Diabetic patients have a unique susceptibility to cardiovascular and renal disease, in addition to other complications such as neuropathy and retinopathy. Once diabetes is established, delaying these complications is challenging, as highlighted by recent trials which have shown no additional protection from very tight glycaemic or blood pressure control compared with conventional management. This is not surprising when considering the natural history of diabetes, which develops over an insidious course, starting with disordered glucose metabolism and a prediabetic period, characterized by IGT and IFG. Diabetes is diagnosed when β-cells fail to compensate for insulin resistance, potentially after many years of overactivation. At this stage there has already been significant vascular changes and even target organ damage, making risk factor modulation less effective. The key therefore is to prevent progression of glucose dysregulation, and ideally correct and reverse any disorder of glucose homeostasis at the earliest possible stage. The close association between obesity and prediabetes, as illustrated by MetS, creates an opportunity to identify 'at risk' individuals through simple anthropometric parameters. Targeted investigation would then permit assessment of FPG, OGTT and HbA1c to diagnose prediabetes through IGT/IFG. This should of course be within the context of comprehensive cardiometabolic risk assessment.

Although guidelines do exist for diagnosing prediabetes, further studies are needed to determine the cost-effectiveness of screening strategies at a public health level and to formalize risk stratification tools. Trial evidence has shown that metabolic disturbances can be halted and regressed with drug therapies and particularly effective diet and lifestyle modification. This should be translated into everyday clinical practice, where the focus is on effective early glycaemic control, with proactive cardiovascular risk reduction. Of the antidiabetic therapies, metformin has been shown to be effective, particularly in overweight individuals, albeit less effective than successful lifestyle change. Although many anti-obesity medications have shown initial promise, such as the neurotransmitter reuptake inhibiters, many have now been withdrawn due to serious adverse effects identified in postmarketing assessment. Newer gastrointestinal lipase inhibitors and other pharmacotherapies targeting gut hormones have shown promise. There is also quite remarkable evidence for the ability of bariatric procedures to reverse metabolic disturbances, but this option is currently specifically indicated for morbidly obese individuals with comorbidities. Future focus should remain on identifying at-risk individuals, diagnosing prediabetes and intervening with effective lifestyle and diet measures, with pharmacology remaining an adjunctive option.

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The authors declare no conflicts of interest in preparing this article.

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