

# The importance of weight management in type 2 diabetes mellitus

J. P. H. Wilding

University Hospital Aintree,  
 Liverpool, UK

**Correspondence to:**

John Wilding, Department of Obesity and Endocrinology, Institute of Ageing & Chronic Disease, Clinical Sciences Centre, University Hospital Aintree, Longmoor Lane, Liverpool, L9 7AL, UK  
 Tel.: + 44(0)151 529 5899  
 Fax: + 44(0)151 529 5888  
 Email: j.p.h.wilding@liv.ac.uk

**Disclosure**

JPHW has received research support from Bristol Myers Squibb, AstraZeneca & Merck Sharpe and Dohme. He has acted as an advisor/consultant to Astellas, AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Lilly, NovoNordisk, Sanofi, & Takeda and has given lectures on behalf of AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Lilly, Merck Sharpe & Dohme, & NovoNordisk. The author was fully responsible for all content and editorial decisions, was involved at all stages of manuscript development and has approved the final version of the review that reflects the author's interpretation and conclusions.

**SUMMARY**

**Background:** The obesity epidemic is driving the increased prevalence of type 2 diabetes mellitus (T2DM), and the vast majority of patients with T2DM are overweight or obese. Excess body weight is associated with the risk of cardiometabolic complications, which are major causes of morbidity and mortality in T2DM. **Aims:** To review evidence about effects of weight loss in pre-diabetes and established T2DM. **Results:** In prediabetes, weight loss has been shown to delay the onset or decrease the risk of T2DM, while in established T2DM weight loss has been shown to improve glycaemic control, with severe calorie restriction even reversing the progression of T2DM. Observational studies support the reduction in cardiovascular risk factors following weight loss in patients with T2DM. However, data from the randomised Look AHEAD trial revealed intensive weight loss interventions did not reduce the rate of cardiovascular events in overweight or obese adults with T2DM, and secondary analyses of other large cardiovascular outcomes trials have also been inconclusive. However, besides cardiovascular risk, other documented benefits of weight loss in T2DM include improvements in quality of life, mobility, and physical and sexual function. **Conclusions:** Physicians should encourage weight loss in all overweight patients with or at risk of T2DM, and should consider the impact on weight when choosing the most appropriate glucose-lowering therapies for these patients.

**Introduction**

The link between weight and type 2 diabetes mellitus (T2DM) is very strong, with studies confirming that the vast majority of patients with T2DM are overweight or obese, and that obese people are at the highest risk of developing T2DM (1). In a meta-analysis of prospective cohort studies from the United States (US) and Europe, obese men had a sevenfold higher risk of developing T2DM, and obese women a 12-fold higher risk, compared with individuals in the healthy weight range (2). Patients were defined as obese based on the widely used cut-off of body mass index (BMI) over 30 kg/m<sup>2</sup>, but similarly increased risks were observed using abdominal obesity, defined by waist circumference of at least 88 cm for women or 102 cm for men (2). For some ethnic

groups, these risks appear to occur at lower levels of BMI, particularly in people of South Asian origin; however, the relationship between weight and T2DM remains (3).

Several studies have shown that obese individuals are also at higher risk of developing cardiovascular disease (CVD) (4), and the risk is even higher in obese people with T2DM (5). A recent survey conducted in Cuba provides a good example of the strong association between population-wide weight change and risk of death from T2DM and CVD (6). The study measured population-wide changes in body weight over time from four large cross-sectional surveys in the years 1991, 1995, 2001 and 2011. Following the Cuban economic crisis of the early 1990s, food and fuel shortages resulted in a decline in energy intake and large increases in physical activity. This was reflected in an

**Review criteria**

- PubMed searches were used to identify clinical trials of weight loss for prevention of type 2 diabetes mellitus (T2DM) and weight loss effects on outcomes in patients with T2DM.
- Relevant articles were identified using search terms including obesity, type 2 diabetes mellitus and cardiovascular, for articles published in English before May 2013.
- Search results were evaluated to identify cardiovascular outcomes studies reporting the association between weight loss and cardiovascular risk in patients with T2DM.

**Message for the clinic**

- For patients with T2DM, the major causes of morbidity and mortality are cardiometabolic complications, which are in themselves associated with excess body weight.
- Although weight loss improves cardiovascular risk factors, it has not been unequivocally demonstrated to reduce cardiovascular event rates.
- While definitive evidence is awaited, physicians should encourage weight loss in all overweight patients with T2DM, especially in light of other benefits of weight loss, such as improvements in mobility.

average population-wide weight loss of 4–5 kg and a decline in death rate from diabetes and CVD. After the crisis, there was a rebound in population weight, followed by a 140% increase in diabetes incidence, and in turn by a 49% increase in the mortality rate from diabetes.

Despite the strong relationship between weight and T2DM, not all individuals who are obese or overweight will develop diabetes, and not all individuals diagnosed with T2DM are overweight. The reported prevalence of lean individuals with T2DM varies in different countries (1,7,8); but even in the United States, where obesity is prevalent, a pooled analysis of five longitudinal studies following 2625 people recently diagnosed with diabetes found about 12% of patients were of normal weight (9). Lean people with diabetes are thought to have a stronger genetic component for T2DM than overweight individuals (10), with researchers hypothesising that the more overweight an individual is, the fewer genetic risk variants are required to predispose them towards diabetes, primarily because they are already under strain from the physiological impact of obesity and insulin resistance (10). This is difficult to prove, and lean T2DM cases are used anecdotally by patients to question the link between obesity and T2DM.

In addition, recent observational studies have reported an 'obesity paradox', in which T2DM patients with normal weight at the time of diagnosis had increased cardiovascular risk, while those who were heavier at diagnosis had a better outcome (9,11). For example, in the US pooled analysis mentioned above, mortality rates were higher in normal-weight participants (284.8 all-cause deaths, 99.8 cardiovascular deaths and 198.1 non-cardiovascular deaths per 10,000 person-years vs. 152.1, 67.8 and 87.9 per 10,000 person-years, respectively, for the same events in overweight or obese participants) (9).

Therefore, although weight loss is recommended by all relevant learned bodies as key to management of T2DM, it remains a controversial area: studies appearing to contradict the link between weight and T2DM are newsworthy, and reports can undermine patient care. In light of this, it is worth taking time to review the trial-based evidence for effects of weight loss in patients with T2DM – are the benefits of weight loss based on assumptions, or does the evidence demonstrate benefit?

## Review methods

In this review, the evidence for the benefits of weight loss in the prevention of T2DM is considered, as well as the relationship between weight loss and glycaemic control, cardiovascular risk, and common

comorbidities in patients with T2DM. Relevant articles were identified by a literature search in PubMed. Further selection of articles was achieved by focusing on large cardiovascular outcomes studies reporting the association between weight loss and cardiovascular risk in patients with T2DM.

### The Look AHEAD study

The Look AHEAD (Action for Health in Diabetes) study exemplifies the kind of attention that surrounds controversial studies of weight and T2DM. The trial was terminated early, announced in a widely reported press release entitled, 'Weight loss does not lower heart disease risk from type 2 diabetes' (12), raising concerns that T2DM patients would abandon their weight loss programs without discussing the details of the trial with their doctor.

The Look AHEAD study was designed specifically to examine the effect of weight loss on a primary outcome of cardiovascular events in overweight and obese patients with T2DM (13). Of 5145 people enrolled at 16 centres across the United States, half were randomly assigned to receive an intensive lifestyle intervention and the other half to a general programme of diabetes support and education. Since it was impractical to mask the intervention, the study was not blinded, but assessments such as waist measurements and weight were made by staff unaware of the assigned groups. Both groups received routine medical care from their own healthcare providers.

Early results were promising, with analysis after 1 year showing a mean 8.6% weight loss with the intensive lifestyle intervention compared with 0.7% for the diabetes support and education group. The additional weight loss was associated with a significant reduction of glycosylated haemoglobin (HbA1c) levels and improvement in several other cardiovascular risk factors compared with the standard group (14), and these results were partly sustained at 4 years (15). Indeed, complete or partial remission of T2DM (defined as glucose normalisation without the need for drugs) was seen in a small proportion of patients in the intensive intervention group ( $p < 0.001$  vs. the standard therapy group) (16). Patients with substantial weight loss or fitness change, shorter duration of diabetes, a lower HbA1c level at entry, and those not using insulin had the highest rates of remission or partial remission (16).

In the intensive lifestyle intervention group, severely obese patients ( $BMI \geq 40 \text{ kg/m}^2$ ) had a similar percentage body weight loss and improvement in cardiovascular risk compared with less obese participants ( $BMI < 40 \text{ kg/m}^2$ ) (17). Across all patients, a correlation seemed to exist between weight loss and improvements in cardiovascular risk factors, with

larger weight losses associated with greater benefits (15). The improvements seen with lifestyle changes outweighed potential genetic association with the risk of T2DM, suggesting intensive lifestyle intervention was worthwhile in all patients (18).

Despite these initial improvements in weight loss, and corresponding improvements in glycaemia and other cardiovascular risk factors, the difference between groups in cardiovascular event rates was lower than expected. The planned follow-up for Look AHEAD was 13.5 years, but in 2012 the trial was halted early, after 9.6 years of follow-up, because there was thought to be little chance of finding the required difference (18%) between the intensive lifestyle intervention and standard care groups (12). Analysis of outcomes reported by the time the trial was stopped showed that major cardiovascular events had occurred in 403 patients in the intensive group compared with 418 in the control group (hazard ratio 0.95; 95% CI, 0.83–1.09,  $p = 0.51$ ). This lack of significant difference was seen despite sustained weight loss over the study: mean weight loss at the end of the trial was 6.0% of body weight in the intensive group vs. 3.5% in the standard group.

It is important to note that a number of factors may have reduced the chances of showing cardiovascular benefit in Look AHEAD. Firstly, the study had been powered to detect a difference of 18% in the rate of major cardiovascular events, using a composite primary outcome of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. However, preliminary analysis after 2 years showed a lower than expected event rate in the standard care group, and hospitalisation for angina was added to the primary outcome, to increase the number of events for analysis. It is notable that there was a numerical (albeit not statistically significant) reduction in the original primary end-point (267 events vs. 283 events) but not for angina (194 events vs. 196 events), suggesting this addition to the end-point could have masked a potential risk reduction. Secondly, during the trial, patients received management of diabetes and cardiovascular risk factors in routine care, and their healthcare providers were not blinded to assigned groups. In the control group, use of potentially cardioprotective agents including metformin, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, and statins was higher, potentially neutralising any effect of weight loss on cardiovascular outcomes. Finally, the weight loss difference between groups was only modest, partly because of regain in the intervention group but also due to the mean 3.5% body weight loss in the control group. However, a weight loss of this magnitude is not typical of routine care, and

may have contributed to the lower than expected event rate in the control group.

Despite these limitations, the early termination of the Look AHEAD study has raised questions as to whether weight loss is an essential component of the management of T2DM. In this review, the evidence for the benefits of weight loss in the prevention of T2DM is considered, as well as the relationship between weight loss and glycaemic control, cardiovascular risk, and common comorbidities in patients with T2DM.

## Benefits of weight loss in the prevention of T2DM

The potential to prevent or delay the onset of T2DM in high-risk individuals through lifestyle interventions such as diet modification, weight reduction and increased physical activity has been established in several clinical trials. Furthermore, follow-up studies show that shorter term interventions can have a long-lasting effect on risk factors and diabetes incidence – the so-called ‘legacy effect’ – years after the lifestyle interventions have finished (19).

Three studies demonstrate this effect clearly. In a trial conducted in 577 adults with impaired glucose tolerance from 33 clinics in Da Qing, China, individuals were randomised to lifestyle intervention (diet only, exercise only, or diet and exercise) for 6 years (between 1986 and 1992), or to a control group (general diabetes counselling). All interventions were associated with a significantly reduced risk of developing diabetes compared with the control group (20). In 2006, a long-term follow-up of the Da Qing group identified a legacy effect, with continued benefits beyond the end of the trial. Compared with the control group, the three intervention groups combined had a 51% reduced incidence of diabetes [95% confidence interval (CI) 27–67%], and a 47% reduction in the incidence of severe, vision-threatening retinopathy over the 20-year interval (95% CI 1–71%) (21,22).

Similarly, in the Finnish Diabetes Prevention Study, adults at high risk of developing T2DM who were randomised to intensive dietary and exercise counselling had a 58% reduction in the risk of developing diabetes after 4 years compared with the usual-care group (who received general information about lifestyle and diabetes risk) (23). Again, a legacy effect was seen after a 13-year follow-up, with intensive lifestyle intervention associated with a significantly reduced risk of developing diabetes. The intensive lifestyle intervention group also sustained lower body weights, fasting plasma glucose (FPG) levels and 2-h postprandial plasma glucose levels (24).

In the United States, the Diabetes Prevention Program study showed that overweight adults who had elevated blood glucose levels (impaired glucose tolerance) could delay the onset of T2DM, or decrease the risk of T2DM, by losing weight (via dietary changes and exercise), with results sustained over a 10-year follow-up period (25,26). In this programme of lifestyle changes, weight loss appeared to be the most important factor in reducing the risk of diabetes when compared with diet composition and increased physical activity (27).

The benefit of weight loss in the prevention of T2DM therefore seems clear, and based on the available evidence, the American Diabetes Association recommend that all patients with impaired glucose tolerance, impaired FPG, or HbA1c 5.7–6.4% should aim for a weight loss of 7% of body weight and increased physical activity to at least 150 min per week of moderate activity (such as walking) to prevent or delay the onset of T2DM (28).

## Benefits of weight loss in the management of T2DM

Given the established advantages of weight loss in patients with prediabetes, it seems intuitive that weight loss will be beneficial in patients with T2DM, not only in terms of glycaemic control, but also other health benefits associated with complications of diabetes. In this section, studies showing effects on glycaemic control are reviewed, before looking in detail at studies of cardiovascular events, and lastly other complications of T2DM.

### Effects on glycaemic control

Weight loss via lifestyle changes is the first-line therapy for T2DM, not for its own sake, but because of the expected improvement in glycaemic control and other associated risk factors (28). The landmark UK Prospective Diabetes Study (UKPDS) clearly demonstrated the benefits of tight glycaemic control (as measured by HbA1c and FPG over prolonged periods). At the time the UKPDS study started (1977), HbA1c had not been widely adopted as the best measure of glucose control, and the World Health Organization then recommended an FPG level of 7.8 mmol/l (140 mg/dl) for the diagnosis of diabetes compared with the current level of 7.0 mmol/l (126 mg/dl) today. The study tested whether treatment to near-normal FPG (< 6.0 mmol/l) would prevent cardiovascular events, using insulin, sulfonylurea, metformin or diet. More than 5000 patients recently diagnosed with T2DM were randomised, and intensive blood glucose control reduced the risk of vascular complications in both the short- and long

term, despite weight gain in the intensive control (insulin/sulfonylurea) group (29). Therefore, if improved glycaemia reduces cardiovascular risk, and weight loss improves glycaemia, weight loss would be expected to provide long-term benefits to patients.

In overweight and obese individuals with T2DM, even modest amounts of weight loss (approximately 5% of body weight) have been shown to improve glycaemic control (30). Longitudinal cohort studies indicate that changes in BMI among patients with T2DM are significant predictors of changes in HbA1c (31), and patients who lose weight are more likely to achieve target HbA1c values than those with stable weight or weight gain (32).

Analyses of randomised trials and observational studies have shown that dietary advice is associated with decreases in HbA1c ranging from 0.25% to 2.9% after 3–6 months, with larger reductions seen in patients more recently diagnosed with T2DM (33). In UKPDS, weight loss in newly diagnosed patients with T2DM improved FPG levels, although a relatively large weight loss was required to reach target FPG levels; for example, weight loss of 28% of ideal body weight (18 kg) was needed in those with a baseline FPG between 10 and 12 mmol/l (34). The link between weight loss and improvements in glycaemic control is further supported by clinical trials with weight-loss medications in patients with T2DM, which have shown significant reductions in HbA1c and FPG (35,36).

At more extreme levels, dietary energy restriction with a very low calorie diet (600 k/cal day) for 8 weeks normalised beta-cell function and resulted in a reversal of T2DM (37). Most patients would find it impossible to follow this type of diet long term, but bariatric surgery (or metabolic surgery as it is sometimes termed when used for treatment of T2DM) has the potential to offer large and durable weight loss that can significantly improve glycaemic control in severely obese patients with T2DM (38,39) or even induce reversal of T2DM (40,41). While this clearly demonstrates the effect of weight loss on glycaemia, long-term follow-up data are needed before this approach can be more widely recommended, as discussed later.

Although there are an increasing number of pharmacotherapy options available to help control glycaemia in patients with T2DM, improvement with diet and exercise offers several potential benefits over pharmacotherapy. These include reduced medication costs as well as clinical benefits, such as avoidance of drug-related adverse effects and reduced risk of hypoglycaemia, a common problem with several therapeutic options, notably sulfonylureas and insulin (42).

### Effects on cardiovascular events

Available evidence from observational studies appears to support a reduced risk of cardiovascular events following weight loss in patients with T2DM. For example, in a prospective analysis of 4970 overweight individuals with diabetes (not identified as type 1 or type 2) with a 12-year follow-up during 1959–1972, weight loss was associated with a 25% reduction in total mortality [relative risk (RR) 0.75, 95% CI 0.67–0.84] and a 28% reduction in CVD- and diabetes-related mortality (RR 0.72, 95% CI 0.63–0.82) compared with individuals who reported no change in weight (43). The participants had provided information on whether weight loss was intentional, helping to overcome the confounding effect of weight loss resulting from comorbid conditions. Somewhat unexpectedly, it was also noted that weight gain was not associated with an increased risk of mortality, while very large weight losses (> 31 kg) were associated with a small increase in mortality (43).

Only a randomised clinical trial can definitively answer the question of whether weight loss programs reduce the risk of mortality or other outcomes. To date, the Look AHEAD study has been the only trial designed to assess this question but, although this trial showed no beneficial effects, it did have a number of limitations, as discussed above (13). Further trials in this area, if conducted at all, will take many years to complete.

Nevertheless, the designs of pharmacotherapy trials have often allowed secondary or post hoc analyses of the effects of weight loss on cardiovascular events among patients with T2DM. Surprisingly, however, given the clear relationship between weight loss and improvements in glycaemia, the results have not always been predictable.

The PROactive study (PROspective pioglitAZone Clinical Trial In macroVascular Events) was a randomised controlled trial comparing the oral antihyperglycaemic drug pioglitazone (associated with weight gain) vs. placebo in 5238 patients with T2DM and evidence of macrovascular disease (44). Pioglitazone and placebo were each taken in addition to the patients' other glucose-lowering drugs, and patients were followed up for an average of 34 months. The primary end-point (a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle) was not significantly reduced, but pioglitazone treatment was associated with significant reductions in the secondary composite end-point of all-cause mortality, non-fatal myocardial infarction and stroke.

As with intensive insulin/sulfonylurea treatment in the UKPDS study, this effect was seen despite a significant weight gain with pioglitazone [mean increase of 3.6 kg (range –30 to +29 kg) in the pioglitazone group vs. a mean decrease of 0.4 kg (range –36 to +33 kg) in the placebo group], and a post hoc analysis was conducted to determine if body weight and weight change were associated with cardiovascular outcomes (45). Unexpectedly, across both treatment groups, patients who were obese at baseline (BMI 30–35 kg/m<sup>2</sup>) had lower mortality than patients with normal weight (BMI 22–25 kg/m<sup>2</sup>). Weight loss during the trial was also associated with increased risk of all-cause mortality [hazard ratio (HR) per 1% body weight: 1.13, 95% CI 1.11–1.16; *p* < 0.0001] compared with those who maintained stable weight (45). In patients treated with pioglitazone, weight gain was associated with a reduced risk compared with stable weight (HR per 1% weight gain: 0.96, 95% CI 0.92–1.00, *p* = 0.037); however, this reduced risk with weight gain was not observed in the placebo group, or when both groups were combined (45).

Such results could be confounded by unintentional weight loss, likely to be associated with other health problems that could increase cardiovascular risk, and the results do appear to be contradicted by other studies, such as the SCOUT study (Sibutramine Cardiovascular Outcome Trial). This large prospective trial was undertaken to determine whether the weight-loss drug sibutramine or placebo (both in addition to weight management with lifestyle intervention) would reduce cardiovascular morbidity and mortality (46). Patients who were overweight or obese, as well as having other risk factors putting them at high risk for cardiovascular events (aged ≥ 55 years with pre-existing CVD, T2DM or both), were recruited. All screened subjects received sibutramine for 6 weeks, after which 9804 patients were randomised to either sibutramine or placebo; the majority of randomised patients (84%) had T2DM.

After a mean treatment duration of 3.4 years, and despite sustained weight reduction with sibutramine, the risk of cardiovascular events increased by 16% (95% CI 3–31%) with sibutramine vs. placebo. This study led in part to the withdrawal of sibutramine as a weight-loss drug; however, the large data set generated by the study facilitated analyses of weight loss and cardiovascular risk. A post hoc analysis showed that, irrespective of treatment group, there was a relationship between the amount of weight lost during the first 12 months of the study and reduction in risk, with those who had the largest weight loss having the greatest reductions in the absolute risk of primary outcome events. Consistent results were seen whether patients were randomised to placebo or

sibutramine, and whether patients were classified as having mild, moderate, or severe CVD (47). Although more events occurred in the randomised sibutramine group, weight loss of approximately 3 kg during the first 6 weeks appeared to offset this increased event rate (47).

Despite being limited by its post hoc nature, this analysis appears to support the concept that weight loss reduces cardiovascular risk, and this is further supported by studies suggesting the converse – that weight gain may increase cardiovascular risk – as was recently reported for the Action to Control Cardiovascular Risk in Diabetes study (ACCORD).

ACCORD compared a therapeutic strategy aiming for HbA1c targets of < 6.0% against a strategy aiming for an HbA1c value of 7.0–7.9% with the objective of determining if tighter HbA1c control (through more intensive therapy) would reduce cardiovascular risk (48). Contrary to expectations, intensive therapy did not significantly reduce major cardiovascular events; in fact, this approach actually increased mortality, with the intensive HbA1c intervention prematurely terminated because of the higher mortality observed (48). However, a reduction in HbA1c was associated with a lower risk of mortality, suggesting another factor besides the very low HbA1c levels that must have accounted for the increased risk in the intensive-therapy group (49). Weight gain is associated with certain medications used more frequently to achieve intensive glycaemic control (e.g. insulin was given to 77.3% of the intensive therapy group vs. 55.4% of the standard-therapy group). Weight gain was indeed higher in the intensive-therapy group, with mean weight gain at 3 years of 3.5 and 0.4 kg in the respective groups, and weight gain of more than 10 kg more frequent in the intensive-therapy group (48), suggesting that weight change might have contributed to the increased risk. Other factors, particularly hypoglycaemia associated with greater use of insulin and sulfonylureas in the intensively treated group, were also suggested to have contributed to the increased risk; however, a recent post hoc analysis found that patients in the intensive therapy group actually had a lower risk of mortality if they had more hypoglycaemic episodes (50).

### Effect on microvascular outcomes and other comorbidities

Weight loss is considered key to management of T2DM because of the potential to reduce blood glucose; however, weight loss can also impact other health problems commonly associated with T2DM. In addition, weight loss can reduce the need for medications, not only for hyperglycaemia but also for hypertension and hyperlipidaemia (51).

Much of the burden of T2DM comes from the microvascular complications, retinopathy, nephropathy, and peripheral and autonomic neuropathy. The risk of developing these complications is correlated with duration of diabetes, blood glucose control and blood pressure, but is also associated with obesity (52,53). However, as with macrovascular outcomes, the role of weight loss in reducing risk is unclear. At present, there is evidence for beneficial effects of weight loss in overweight patients on proteinuria in non-diabetic renal disease with neuropathy, with weight loss of approximately 4% of body weight associated with decreases of  $31.2 \pm 37\%$  in proteinuria from baseline in a small, 5-month study (54); a reduction in albuminuria was also seen with intensive lifestyle intervention in the Look AHEAD trial (55). Furthermore, meta-analysis of 13 studies of intentional weight loss in patients with chronic kidney disease (with and without diabetes) showed improvements in proteinuria over a mean follow-up of 7.4 months, but long-term studies are needed to determine if this translates to improved clinical outcomes, such as progression to end-stage renal failure (56).

As well as the vascular complications of T2DM, weight loss can improve quality of life and many common comorbidities (57). Obstructive sleep apnoea is recognised to be associated with obesity and diabetes, and the effect of weight loss on obstructive sleep apnoea among obese patients with T2DM was prospectively assessed in the Sleep AHEAD study, a substudy of the Look AHEAD trial, and showed that 20% of patients with sleep apnoea and diabetes had remission of their sleep apnoea over 4 years in the intensive intervention group compared with only 3.6% in the controls (58,59).

The Look AHEAD study also captured outcomes for other comorbidities frequently linked to obesity, and clearly showed that weight loss was associated with improvements in mobility (60) and physical function (61). Among women who participated in the study, weight loss reduced the incidence of urinary incontinence at 1 year, although it did not improve resolution rates (62). In a subgroup of men from five of the centres participating in Look AHEAD, weight loss intervention was associated with maintenance of erectile function (63). However, not all changes with weight loss were positive; of note, weight loss after 1 year appeared to be associated with reduced bone mineral density, despite improved fitness (64).

In patients with prediabetes, weight loss has been associated with improvements in mood (65). The Look AHEAD study also seemed to support this premise in that the intensive lifestyle intervention group

had a significantly lower incidence of potentially significant symptoms of depression (66).

## Effects of glucose-lowering treatments on weight

While lifestyle counselling is the first-line therapy to improve glycaemia in new-onset diabetes, it is unusual for patients to achieve target HbA1c values via weight loss alone. Thus, most patients will require oral glucose-lowering drugs and, because of the progressive nature of T2DM, many patients eventually will require insulin. Although these therapies are effective in reducing HbA1c, many can lead to unwanted weight gain, which could offset the benefits.

Currently, there are several different classes of drugs available to control blood glucose and effects on weight vary among the classes (Table 1). For a patient who needs to avoid weight gain or to lose weight, metformin, any of the dipeptidyl peptidase-4 (DPP-4) inhibitors, bile-acid sequestrants, and alpha-glucosidase inhibitors are weight-neutral (42), and should therefore not offset any lifestyle changes the patient makes. On the other hand, the commonly used second-line drugs, sulfonylureas, are associated with significant weight gain, as are the meglitinides, thiazolidinediones and insulin (42,67).

Of the widely available drug classes, two groups are associated with weight loss. The glucagon-like peptide-1 (GLP-1) receptor agonists are associated with weight reduction of about 3 kg, and are even being assessed as anti-obesity medications in their own right (68,69). GLP-1 receptor agonists reduce

blood glucose by increasing insulin secretion when glucose levels are elevated, but also delay gastric emptying and decrease food intake. GLP-1 receptor agonists are injectable agents, but the possibility of once-weekly injections may make them more attractive to patients and increase adherence, while oral options are the focus of intensive research, although not likely to be available for some years (70,71). The recent approval of the first agents of a new drug class, the sodium glucose co-transporter 2 (SGLT2) inhibitors, offers the promise of oral glucose-lowering drugs associated with weight reduction (72). These drugs work by increasing the excretion of glucose in urine, with resulting excretion of the corresponding calories. Early studies suggest SGLT2 inhibitors may even help offset the weight gain associated with other glucose-lowering therapies, particularly insulin (73). The mechanism of weight reduction, by increasing urinary excretion of glucose, has created the perception that the weight reduction may be via water loss as well as lost calories, but studies have shown reductions in both visceral and subcutaneous adipose tissue (74,75). The SGLT2 inhibitors may therefore be a useful option in overweight patients; however, as they are a new class of glucose-lowering drugs it remains to be seen whether they will provide sustained benefit on weight and help reduce long-term complications of diabetes.

## The role of anti-obesity medications in the management of T2DM

If the primary reason for lifestyle change to promote weight loss in patients with T2DM is ultimately to help reduce HbA1c and improve other risk factors, it is reasonable to consider the effects of drugs that have a primary effect on body weight rather than glucose control in patients with T2DM. At present, three pharmacological options are available in the United States for the treatment of obesity: orlistat (approved 1999), lorcaserin (approved 2012) and the combination therapy of phentermine plus topiramate (approved 2012). Of these, only orlistat is licensed in Europe, and the US Food and Drug Administration has requested long-term trials of lorcaserin and phentermine plus topiramate to determine the cardiovascular safety of these compounds, suggesting that they should be used with caution.

These drugs have been primarily tested in patients with obesity alone, and to date, only one study has reported the use of lorcaserin in T2DM. In that study, a 1-year, randomised, placebo-controlled trial enrolling 604 patients, lorcaserin was associated with modest weight loss (3 kg different from placebo at the highest dose) and improvement in glycaemic control

**Table 1** Effects of glucose-lowering medications on weight

Drug class	Weight effects
<b>Injectable agents</b>	
Insulin	+*
Amylin mimetics	–
GLP-1 mimetics	–
<b>Oral agents</b>	
Sulfonylureas	+*
Meglitinides	+
Thiazolidinediones	+*
Biguanides	Neutral
Alpha-glucosidase inhibitors	Neutral
DPP-4 inhibitors	Neutral
Bile-acid suppressants	Neutral
D <sub>2</sub> -dopamine receptor agonists	Neutral
SGLT2 inhibitors	–

–, Weight loss; +, Weight gain. \*Substantial increase in some patients.

(0.5% difference from placebo) (76). Studies of phentermine plus topiramate in patients with T2DM have not yet been reported, but in obese patients (without T2DM), phentermine plus topiramate demonstrated sustained weight loss associated with decreased rates of incident diabetes compared with placebo (77).

As orlistat has been available for several years, several studies have examined its effects in patients with T2DM. In a 1-year, randomised, placebo-controlled trial enrolling 254 obese patients with T2DM, orlistat improved measures of insulin resistance, as well as glycaemia and weight, vs. placebo (78). In a 24-week, randomised, placebo-controlled trial in 249 patients newly diagnosed with T2DM and who were treatment-naïve, orlistat (in combination with a reduced-calorie diet) significantly reduced body weight and improved glycaemic control vs. placebo (79). In a 1-year, randomised, placebo-controlled trial, patients with T2DM treated with either metformin alone or metformin in combination with a sulfonylurea were randomised to double-blind treatment with orlistat or placebo. After 1 year, orlistat-treated patients achieved an almost threefold greater reduction in weight compared with placebo recipients (−5.0% vs. −1.8%;  $p < 0.0001$ ). The orlistat group also had improvements in HbA1c, FPG, and markers of beta-cell function compared with placebo (80).

Based on these findings, the Look AHEAD investigators concluded that orlistat could be used as an adjunct to the study's weight-maintenance program, but 'clearly was not a substitute for participants' continued efforts to increase their physical activity and control their calorie intake' (81). It could be offered to individuals who failed to meet the study's weight-loss goals in the first 6 months (or to those who subsequently regained weight). However, the use of orlistat was largely discontinued during the study, after interim analyses showed that it had limited effectiveness as a rescue therapy (82). Therefore, while all available weight-loss drugs show some promise in the management of obese patients with T2DM, their exact role is as yet uncertain.

## The role of bariatric surgery

Bariatric surgery can be an effective way of obtaining weight loss for people with T2DM and more severe obesity (83). Evidence from the observational SOS (Swedish Obese Subjects) study showed that in those with diabetes, weight loss from Roux-en-Y gastric bypass, adjustable gastric banding, or the now obsolete vertical banded gastroplasty could reduce weight by approximately 20–30 kg over 10 years with substantial lowering of blood glucose and a reduction in cardiovascular mortality (84). Recent studies com-

paring surgery to conventional diabetes treatment suggest that better glycaemic control can be achieved with surgery, with a substantial proportion of patients developing prolonged remission from diabetes (40,41). There is also evidence of benefit of surgery in patients who are less obese, with a few small trials supporting the use of surgery in patients with BMI in the range 30–35 kg/m<sup>2</sup> (83,85). At present, most surgery is reserved for patients with more severe obesity, but these findings do provide further evidence of the benefits of weight loss in T2DM, and guidelines for the use of bariatric surgery may be updated in the near future (86).

## Conclusion

The increase in the number of overweight or obese people is strongly linked to the increasing prevalence of T2DM. Furthermore, obesity is an independent risk factor for hypertension and dyslipidaemia as well as CVD, which is the major cause of death in patients with T2DM, and weight loss is considered key to the management of T2DM. In patients with prediabetes, there is clear evidence that moderate weight loss can prevent the development of T2DM. In patients with established T2DM, the evidence is less clear-cut: the link between weight loss and improvements in glycaemic control and other risk factors is well established, but there is only indirect evidence that weight loss reduces the risk of cardiovascular events, and as yet there is little information with regard to the microvascular complications of diabetes.

The recent result from the Look AHEAD study suggests that modest weight loss may not have clear benefits for cardiovascular protection in T2DM, or at least that these will be hard to demonstrate in lifestyle intervention studies. Ideally, future studies will be designed to ensure clinical differences in weight loss as well as balanced use of other cardioprotective interventions. The benefits of weight loss on other aspects of health and quality of life in overweight or obese people with T2DM are, however, undeniable. In light of this, physicians should encourage weight loss in all patients with or at risk of T2DM, and should consider the impact on weight when choosing the most appropriate glucose-lowering therapies for these patients.

## Acknowledgements

Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Geraldine Thompson of Envision Scientific Solutions during the preparation of this review. Boehringer Ingelheim was given the opportunity to check the data used in the manuscript for factual accuracy only.



## References

- 1 Daouisi C, Casson IF, Gill GV, et al. Prevalence of obesity in type 2 diabetes in secondary care: association with cardiovascular risk factors. *Postgrad Med J* 2006; **82**: 280–4.
- 2 Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health* 2009; **9**: 88.
- 3 Chiu M, Austin PC, Manuel DG, et al. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. *Diabetes Care* 2011; **34**: 1741–8.
- 4 Bogers RP, Bemelmans WJ, Hoogenveen RT, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med* 2007; **167**: 1720–8.
- 5 Jonsson S, Hedblad B, Engstrom G, et al. Influence of obesity on cardiovascular risk. Twenty-three-year follow-up of 22,025 men from an urban Swedish population. *Int J Obes Relat Metab Disord* 2002; **26**: 1046–53.
- 6 Franco M, Bilal U, Ordunez P, et al. Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980–2010: repeated cross sectional surveys and ecological comparison of secular trends. *BMJ* 2013; **346**: f1515.
- 7 Gregg EW, Cheng YJ, Narayan KM, et al. The relative contributions of different levels of overweight and obesity to the increased prevalence of diabetes in the United States: 1976–2004. *Prev Med* 2007; **45**: 348–52.
- 8 Yano Y, Sato Y, Fujimoto S, et al. Association of high pulse pressure with proteinuria in subjects with diabetes, prediabetes, or normal glucose tolerance in a large Japanese general population sample. *Diabetes Care* 2012; **35**: 1310–5.
- 9 Carnethon MR, De Chavez PJ, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. *JAMA* 2012; **308**: 581–90.
- 10 Perry JR, Voight BF, Yengo L, et al. Stratifying type 2 diabetes cases by BMI identifies genetic risk variants in LAMA1 and enrichment for risk variants in lean compared to obese cases. *PLoS Genet* 2012; **8**: e1002741.
- 11 McEwen LN, Karter AJ, Waitzfelder BE, et al. Predictors of mortality over 8 years in type 2 diabetic patients: Translating Research Into Action for Diabetes (TRIAD). *Diabetes Care* 2012; **35**: 1301–9.
- 12 National Institutes of Health. Weight loss does not lower heart disease risk from type 2 diabetes. 2012 <http://www.nih.gov/news/health/oct2012/niddk-19.htm> (accessed January 21, 2013).
- 13 Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369**: 145–54.
- 14 Pi-Sunyer X, Blackburn G, Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. *Diabetes Care* 2007; **30**: 1374–83.
- 15 Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011; **34**: 1481–6.
- 16 Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012; **308**: 2489–96.
- 17 Unick JL, Beavers D, Jakicic JM, et al. Effectiveness of lifestyle interventions for individuals with severe obesity and type 2 diabetes: results from the Look AHEAD trial. *Diabetes Care* 2011; **34**: 2152–7.
- 18 Peter I, McCaffery JM, Kelley-Hedgpeath A, et al. Association of type 2 diabetes susceptibility loci with one-year weight loss in the look AHEAD clinical trial. *Obesity (Silver Spring)* 2012; **20**: 1675–82.
- 19 Tuomilehto J, Schwarz P, Lindstrom J. Long-term benefits from lifestyle interventions for type 2 diabetes prevention: time to expand the efforts. *Diabetes Care* 2011; **34**(Suppl. 2): S210–4.
- 20 Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; **20**: 537–44.
- 21 Gong Q, Gregg EW, Wang J, et al. Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. *Diabetologia* 2011; **54**: 300–7.
- 22 Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008; **371**: 1783–9.
- 23 Lindstrom J, Louheranta A, Manninen M, et al. The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 2003; **26**: 3230–6.
- 24 Lindstrom J, Peltonen M, Eriksson JG, et al. Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). *Diabetologia* 2013; **56**: 284–93.
- 25 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393–403.
- 26 Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; **374**: 1677–86.
- 27 Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006; **29**: 2102–7.
- 28 American Diabetes Association. Standards of medical care in diabetes – 2013. *Diabetes Care* 2013; **36**(Suppl. 1): S11–66.
- 29 Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**: 1577–89.
- 30 Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord* 1992; **16**: 397–415.
- 31 Ridderstrale M, Gudbjornsdottir S, Eliasson B, et al. Obesity and cardiovascular risk factors in type 2 diabetes: results from the Swedish National Diabetes Register. *J Intern Med* 2006; **259**: 314–22.
- 32 Feldstein AC, Nichols GA, Smith DH, et al. Weight change in diabetes and glycemic and blood pressure control. *Diabetes Care* 2008; **31**: 1960–5.
- 33 Pastors JG, Warshaw H, Daly A, et al. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care* 2002; **25**: 608–13.
- 34 UK Prospective Diabetes Study (UKPDS) Group. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. *Metabolism* 1990; **39**: 905–12.
- 35 Norris SL, Zhang X, Avenell A et al. Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2005; **1**: CD004096.
- 36 Vettor R, Serra R, Fabris R, et al. Effect of sibutramine on weight management and metabolic control in type 2 diabetes: a meta-analysis of clinical studies. *Diabetes Care* 2005; **28**: 942–9.
- 37 Lim EL, Hollingsworth KG, Arribasala BS, et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011; **54**: 2506–14.
- 38 Dixon JB, Zimmet P, Alberti KG, Rubino F. Bariatric surgery: an IDF statement for obese type 2 diabetes. *Diabet Med* 2011; **28**: 628–42.
- 39 Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA* 2013; **309**: 2240–9.
- 40 Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012; **366**: 1577–85.
- 41 Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012; **366**: 1567–76.
- 42 Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; **35**: 1364–79.
- 43 Williamson DF, Thompson TJ, Thun M, et al. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care* 2000; **23**: 1499–504.
- 44 Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366**: 1279–89.
- 45 Doehner W, Erdmann E, Cairns R, et al. Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: an analysis of the PROactive study population. *Int J Cardiol* 2012; **162**: 20–6.
- 46 James WP, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; **363**: 905–17.

- 47 Caterson ID, Finer N, Coutinho W, et al. Maintained intentional weight loss reduces cardiovascular outcomes: results from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial. *Diabetes Obes Metab* 2012; **14**: 523–30.
- 48 Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–59.
- 49 Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glyemic treatment in the ACCORD trial. *Diabetes Care* 2010; **33**: 983–90.
- 50 Seaquist ER, Miller ME, Bonds DE, et al. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. *Diabetes Care* 2012; **35**: 409–14.
- 51 Redmon JB, Bertoni AG, Connelly S, et al. Effect of the look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. *Diabetes Care* 2010; **33**: 1153–8.
- 52 Smith AG, Singleton JR. Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. *J Diabetes Complications* 2013; **27**: 436–42.
- 53 Igarashi T, Kawato H, Kamoshita S, et al. Acute tubulointerstitial nephritis with uveitis syndrome presenting as multiple tubular dysfunction including Fanconi's syndrome. *Pediatr Nephrol* 1992; **6**: 547–9.
- 54 Morales E, Valero MA, Leon M, et al. Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *Am J Kidney Dis* 2003; **41**: 319–27.
- 55 Kramer H, Reboussin D, Bertoni AG, et al. Obesity and albuminuria among adults with type 2 diabetes: the Look AHEAD (Action for Health in Diabetes) Study. *Diabetes Care* 2009; **32**: 851–3.
- 56 Navaneethan SD, Yehner H, Moustarah F, et al. Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2009; **4**: 1565–74.
- 57 Shah K, Villareal DT. Weight loss and improved fitness slow down the decline in mobility in obese adults with type 2 diabetes. *Evid Based Med* 2012; **18**: e18.
- 58 Foster GD, Borradaile KE, Sanders MH, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med* 2009; **169**: 1619–26.
- 59 Kuna ST, Reboussin DM, Borradaile KE, et al. Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. *Sleep* 2013; **36**: 641–9A.
- 60 Rejeski WJ, Ip EH, Bertoni AG, et al. Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med* 2012; **366**: 1209–17.
- 61 Foy CG, Lewis CE, Hairston KG, et al. Intensive lifestyle intervention improves physical function among obese adults with knee pain: findings from the Look AHEAD trial. *Obesity (Silver Spring)* 2011; **19**: 83–93.
- 62 Phelan S, Kanaya AM, Subak LL, et al. Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD trial. *J Urol* 2012; **187**: 939–44.
- 63 Wing RR, Rosen RC, Fava JL, et al. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD trial. *J Sex Med* 2010; **7**: 156–65.
- 64 Schwartz AV, Johnson KC, Kahn SE, et al. Effect of 1 year of an intentional weight loss intervention on bone mineral density in type 2 diabetes: results from the Look AHEAD randomized trial. *J Bone Miner Res* 2012; **27**: 619–27.
- 65 Ruusunen A, Voutilainen S, Karhunen L, et al. How does lifestyle intervention affect depressive symptoms? Results from the Finnish Diabetes Prevention Study. *Diabet Med* 2012; **29**: e126–32.
- 66 Faulconbridge LF, Wadden TA, Rubin RR, et al. One-year changes in symptoms of depression and weight in overweight/obese individuals with type 2 diabetes in the Look AHEAD study. *Obesity (Silver Spring)* 2012; **20**: 783–93.
- 67 Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; **361**: 1736–47.
- 68 Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)* 2012; **36**: 843–54.
- 69 Vilsboll T, Christensen M, Junker AE, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2012; **344**: d7771.
- 70 Willard FS, Sloop KW. Physiology and emerging biochemistry of the glucagon-like peptide-1 receptor. *Exp Diabetes Res* 2012; **2012**: 470851.
- 71 Grunberger G, Chang A, Garcia Soria G, et al. Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycaemic control in a randomized, double-blind, placebo-controlled study. *Diabet Med* 2012; **29**: 1260–7.
- 72 Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open* 2012; **2**: e001007.
- 73 Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med* 2012; **156**: 405–15.
- 74 Bolinder J, Ljunggren O, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycaemic control on metformin. *J Clin Endocrinol Metab* 2012; **97**: 1020–31.
- 75 Grempler R, Thomas L, Sauer A et al. The novel SGLT-2 inhibitor BI 10773 (empagliflozin) prevents pioglitazone-induced weight gain and further improves glycaemic control in dietary-induced obese rats 2011. Abstract presented at the American Diabetes Association 71st Scientific Sessions, San Diego, California, 24–28 June 2011, abstract # 1851-P.
- 76 O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012; **20**: 1426–36.
- 77 Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr* 2012; **95**: 297–308.
- 78 Derosa G, Cicero AF, D'Angelo A, et al. Effects of 1-year orlistat treatment compared to placebo on insulin resistance parameters in patients with type 2 diabetes. *J Clin Pharm Ther* 2012; **37**: 187–95.
- 79 Shi YF, Pan CY, Hill J, Gao Y. Orlistat in the treatment of overweight or obese Chinese patients with newly diagnosed type 2 diabetes. *Diabet Med* 2005; **22**: 1737–43.
- 80 Berne C. A randomized study of orlistat in combination with a weight management programme in obese patients with type 2 diabetes treated with metformin. *Diabet Med* 2005; **22**: 612–8.
- 81 Wadden TA, West DS, Delahanty L, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)* 2006; **14**: 737–52.
- 82 Wadden TA, West DS, Neiberg RH, et al. One-year weight losses in the Look AHEAD study: factors associated with success. *Obesity (Silver Spring)* 2009; **17**: 713–22.
- 83 Maggard-Gibbons M, Maglione M, Livhits M, et al. Bariatric surgery for weight loss and glycaemic control in nonmorbidly obese adults with diabetes: a systematic review. *JAMA* 2013; **309**: 2250–61.
- 84 Romeo S, Maglio C, Burza MA, et al. Cardiovascular events after bariatric surgery in obese subjects with type 2 diabetes. *Diabetes Care* 2012; **35**: 2613–7.
- 85 Cohen RV, Pinheiro JC, Schiavon CA, et al. Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. *Diabetes Care* 2012; **35**: 1420–8.
- 86 Cummings DE, Cohen RV. Response to comment on: Cohen et al. Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. *Diabetes Care* 2012; **35**: 1420–1428; *Diabetes Care* 2013; **36**: e59.

Paper received October 2013, accepted December 2013