REVIEW ARTICLE

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Editor's Choice

The importance of weight management in type 2 diabetes mellitus

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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.

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.

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^2, 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

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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 kg/m^2) had a similar percentage body weight loss and improvement in cardiovascular risk compared with less obese participants (BMI $<$ 40 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^2) had lower mortality than patients with normal weight (BMI 22–25 kg/m^2). 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

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