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VLED and formula LED in the management of type 2 diabetes: defining the clinical need and research requirements

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Summary

It has been known for many years that substantial weight loss, achieved by bariatric surgery or non-surgical means can mean normalize glucose tolerance. Recent randomized controlled trial evidence indicates that >15 kg weight loss is necessary, to this and it may lead to near normalization (doubling) of life expectancy. Less than 5% of patients achieve this through even the best, evidence-based medical weight management programme (Counterweight http://www.counterweight.org).

A weight loss of >15 kg is easily achievable by 8 weeks very low-energy diet (VLED)/LELD (Low energy Liquid-formula Diet) in compliant patients, with little difference between 400 and 800 kcal day^{-1}, but weight maintenance after VLED has until recently been so poor that VLED is not, at present, recommended in clinical guidelines. However, mean weight loss close to >15 kg can be maintained 18–24 months using a variety of maintenance strategies. These include a structured reintroduction of foods linked to an education programme with behavioural strategies, intermittent VLED use and prescribable anti-obesity drugs (dexfenfluramine, orlistat, sibutramine). Most of these studies have been in non-diabetic subjects.

A new 'curative' paradigm in type 2 diabetes mellitus management, aiming to normalize glucose tolerance and health risks by achieving and maintaining >15 kg loss, as soon as possible after diagnosis, should be highly acceptable to patients, generating many additional Quality Adjusted Life Years (QALYs). It is likely to be highly cost-effective by avoiding the current recommended, mainly palliative, model, using polypharmacy which provides an overall risk reduction of only 5–10%.

Clinical trials are on-going to establish the feasibility of delivering formula (LELD) and a maintenance programme to large numbers of patients within routine primary care. There is urgent need, to run similar studies in diabetic patients. New approaches to long-term (lifelong) maintenance of weight loss and a non-diabetic state may include anti-obesity drugs.

Keywords: Guideline, obesity, weight loss.

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Introduction

Over the past 100 years paradigms for the management of type 2 diabetes mellitus (T2DM) have cautiously edged from purely symptom-relief (glucose lowering) firstly towards microvascular risk reduction (glucose normalizing, blood pressure [BP] lowering) and most recently towards a focus on macrovascular risk reduction (combined glucose, BP and lipid lowering, anti-thrombotic treatments). This progress based on clearer recognition of the clinical impact of diabetes, has unfortunately led to a situation where most T2DM patients are soon prescribed, according to current

Table 1 Palliative polypharmacy for type 2 diabetes based on National Institute for Health and Clinical Excellence/Scottish Intercollegiate Guidelines Network evidence-based guidelines

Metformin
±Insulin/SU (Sulphonylurea) glitazone/gliptin/GLP-1 (Glucagon-like Peptide-1) agonist
Statin
ACE (Angiotensin-converting Enzyme) inhibitor
±calcium channel inhibitor
Beta-blocker
Furosemide
Aspirin ± omeprazole

Table 2 What the clinical guidelines say

SIGN 2010 – Obesity, No 115
Key recommendation 2.2
'in patients with **BMI > 35 kg m^{-2}** obesity-related comorbidities are likely to be present therefore weight loss interventions should be targeted to improving these comorbidities; in many individuals a **greater than 15–20% weight loss** (will always be over 10 kg) will be required to obtain a sustained improvement in comorbidity'

BMI, body mass index; SIGN, Scottish Intercollegiate Guidelines Network.

evidence-based guidelines, six to eight different drugs every day for life (Table 1). Their combined effect has been estimated to reduce cardiovascular disease risks by only about 5–10%. Many patients already have or soon develop onset cardiovascular disease, requiring further drug treatment, e.g. anti-anginal, as well as drugs for other obesity-induced problems (arthritis, depression, etc.). Thus many T2DM patients are prescribed 8–12 drugs, but the underlying disease process continues. The risk of T2DM is exceedingly low at body mass index (BMI) 21–22, but rises to five times this level with BMI 25, about 30 times this level with BMI 30 and relative risk rises to almost 100 with BMI above 35 (1). The lifetime risk of T2DM is greater for those who become obese at a young age, but the effect is seen into old age. With BMI > 35, the remaining average lifetime risk of T2DM is 79% at 18, 60% at age 45 and 35% at age 65 (2). This makes T2DM the disease most strongly linked with weight gain and obesity, and from first principles the argument is unassailable that weight management should be the primary avenue of treatment. If weight loss and maintenance is not possible, then it remains valuable to add more palliative drug treatments.

Although the development of T2DM depends on weight gain and obesity, and all its pathogenic consequences are prevented or reversed by weight loss, weight management receives little more than lip-service in most clinical guidelines and diabetes care services. For example, Scottish Intercollegiate Guidelines Network (SIGN) diabetes (3) offers no target, and no recommended weight management approach, but refers to the SIGN Obesity Guideline (4) which does not contain any guidance for weight management in diabetes, although it does recommend more intensive interventions for severe and complicated obesity (Table 2). The International Diabetes Federation global guideline offers no target (5,6). It is still considered difficult, or a waste of time to provide effective weight management even though modest, achievable weight loss (5–10 kg) has been shown to bring major clinical benefits. Many patients with T2DM never see a dietitian (7). Patients want to lose weight, but find insufficient value from the effort required for them to sustain this degree of loss, and seek greater loss (8,9).

In principle, a very low-energy diet (VLED)/LELD supplying only 400–800 kcal day^{-1} will induce an energy deficit of 2000–3000 kcal day^{-1} for any severely obese patient – and more if the patient is extremely obese, or is physically active. Any patient who is fully compliant with VLED/LELD will thus lose 2–3 kg week^{-1}, even allowing for the compensatory temporary fall in metabolic rate (10,11). There is usually more rapid loss in the first week, through glycogen depletion and water loss. This degree of energy defect and obligatory weight loss is very similar to that in the early months after bariatric surgery. The only difference is that surgery usually provides a physical obstacle to excessively increased intake and regain.

Bariatric surgery has been promoted as a treatment for T2DM, by bariatric surgeons and their patients, for many years. As long ago as 1992 Pories and colleagues published their data on 288 patients with diabetes or glucose tolerance, of whom 258 reverted to normal glucose tolerance, with the conclusion 'Diabetes is a surgical disease' (12). More recently a colossal systematic review and meta-analysis concluded that some 75% would be restored to a non-diabetic state by bariatric surgery (13). Suspicion about the uncontrolled nature of these data precluded this evidence being included in guidelines for diabetes care. However, the results were essentially identical to those published from the Swedish Obese Subjects which did have a non-intervention control group (14), and any doubt has been erased by a well-conducted randomized controlled trial (RCT) which again showed 73% of T2DM (diagnosed less than 2 years) reverted to normal glucose tolerance at 2 years following laparoscopic banding surgery (15). The claim of surgeons that this is a 'cure' may be true for many, although it is possible that metabolism will slip back to a diabetic state at some future stage. However, normal glucose tolerance means freedom from stigmatization and insurance penalties, freedom from complications of diabetes, and freedom from the need for lifelong expensive and intrusive palliative treatments.

A new target – 15 kg loss

A key observation from the RCT of bariatric surgery for obese patients with T2DM, is that resolution of diabetes to

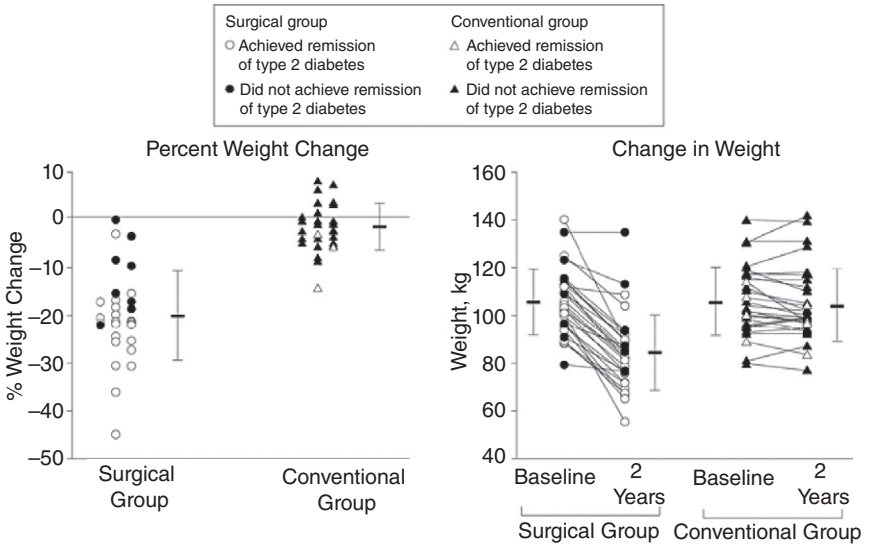

Figure 1 Percentage of weight loss achieved over the 2-year study period ($n = 60$) and individual weight measures at baseline and at 2 years. Remission indicates those achieving remission of type 2 diabetes (see *Methods*) at 2 years. Data markers with error bars indicate mean (SD) (Dixon *et al.* (15)).

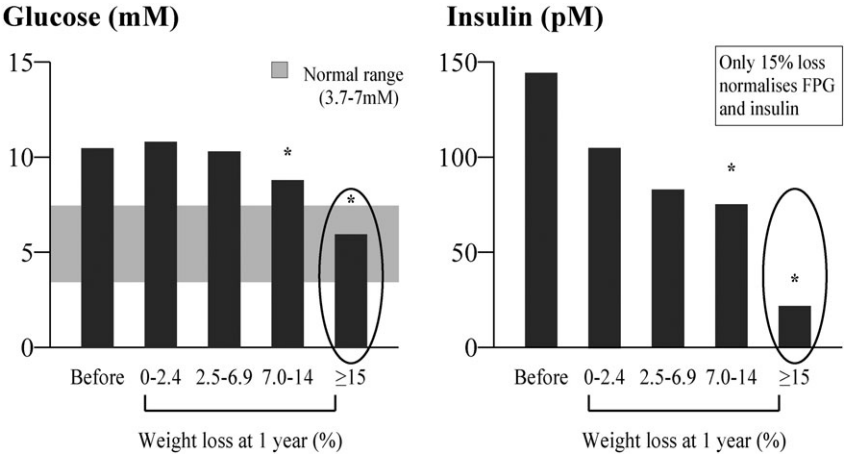

Figure 2 Weight change and glycaemic control at 12 months in obese patients with type 2 diabetes mellitus (T2DM) (adapted from Wing *et al.*; Klein S (16,17)).

normal glucose tolerance, at 2 years, occurred almost exclusively in those patients who lost and maintained >15 kg below baseline (in both surgical and medical control groups) (15). Those who maintained less than 15 kg loss at 2 years failed to achieve normal glucose tolerance (Fig. 1) (15). The results should not be extrapolated to all T2DM patients. They were a relatively young and otherwise healthy group. Importantly, they were treated within 2 years of diagnosis of T2DM – before serious depletion of beta-cell reserves.

This treatment threshold of 15 kg loss appears to be a new clinical reality for patients with severe and complicated obesity, as the amount needed to reverse the most intractable complication of obesity. There are few hazards to patients in losing >15 kg, and many other benefits accrue, so this seems a reasonable target for weight management. It is supported by other non-surgical weight loss data. Wing *et al.* and Klein showed improved diabetic control with weight loss and weight loss of ≥15 kg resulted in normalization of both glucose and insulin (Fig. 2) (16,17). The VLED leads to a very rapid improvement in glycaemia, with normalization as soon as 2 weeks shown in a meta-analysis by Anderson *et al.* (18). Intentional weight loss has been shown in several studies to be associated with increased survival in patients with T2DM (19,20).

Life expectancy is reduced 5–20 years by T2DM, through increased coronary heart disease (CHD) × 2–3, cancers, and infections and obesity aggravates all the risk factors so life expectancy is further reduced. At age 64, the mean life expectancy in an unselected clinic population with T2DM is only 6–8 years, which compares with 12–15 years in non-diabetic people of the same age locally (19,21). The clinical audit of Lean *et al.* (19) had particular statistical strength in having followed up from diagnosis to death a cohort defined by year of death. The numbers of patients who lost over 12 kg under the clinic dietitian was too small to make confident predictions, but an extrapolation of the study results suggested that survival would be

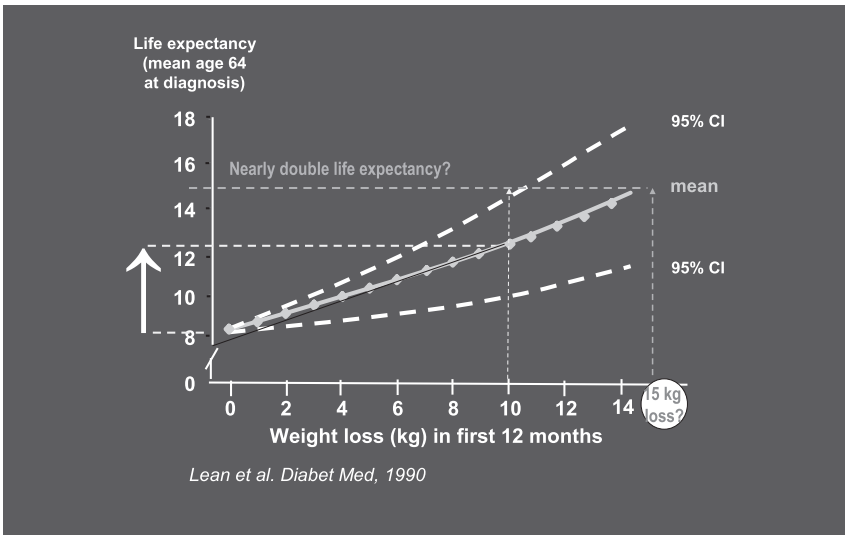

Figure 3 Modest intentional weight loss increases life expectancy for overweight T2DM (Lean *et al.* (19)).

increased by 8 years with 15 kg loss – restoring the life expectancy of those overweight T2DM patients close to the level expected for non-diabetic patients of the same age (mean age 64 at diagnosis) (Fig. 3).

In principle, it is therefore reasonable to expect that for most patients weight loss >15 kg achieved by any means, would restore patients with recent onset of T2DM to normal glucose tolerance, and avoid or at least delay appallingly all the clinical consequences of diabetes. It is already well established that weight loss has a more dramatic effect than any oral hypoglycaemic on glycaemic drugs and can normalize the dyslipidaemia of T2DM (18) and lowers the blood pressure of hypertensive patients more than any hypertensive drug. These metabolic effects of weight loss are all sustained for at least 10 years, if weight gain is provided, with the possible exception of the hypotensive effect (14,22).

On these grounds, the evidence is very persuasive that effective and sustained weight loss at diagnosis with a target >15 kg, should be recommended as the top priority in managing T2DM. The timing of treatment may be important, as a failure to lose weight leaves the underlying disease process, which progresses to beta-cell loss such that restoration of normal glucose tolerance will become less likely. From the patients' perspective, restoration of normal glucose tolerance which would also be accepted as a 'cure' for insurance purposes should be very attractive. The alternative management for T2DM, as currently recommended by guidelines, is essentially palliative. Patients with T2DM are given only token or very general advice for weight loss (3,23) and are frequently prescribed six to eight 'diabetes-related' drugs to take daily – or more if they are hypertensive. These drugs are based on evidence that blood glucose lowering has a modest effect in delaying macrovascular complications of diabetes (and a cocktail of lipid-lowering, anti-thrombotic and anti-hypertensive drugs reduces the risk of CHD). The net effect of this polypharmacy is to reduce the overall CHD risk of T2DM patients by just 5–10% (24,25). These drugs are prescribed for life, and can cause side effects. Obese diabetic patients can expect also to need other drugs for conditions caused or aggravated by obesity, such as H_2-blockers, analgesics for arthritis or back pain, diuretics, anti-anginals and antidepressants. It is thus not uncommon for obese T2DM patients to be prescribed 8–12 drugs and some more. Patients commonly do not take this medication (26). Most, including all the medication for diabetes could become unnecessary with sufficient weight loss.

There are multiple clinical benefits affecting many body systems from weight loss (Fig. 4) (27). These benefits will accrue for obese T2DM patients just as for anyone else, and outweigh the fairly small risk of clinical hazards of major weight loss, such as symptomatic gall stones which develop in about 5–10% (28).

Combining treatments for weight management for type 2 diabetes mellitus

Clinical guidelines have identified three aims of weight management which need to be addressed separately: initial weight loss, long-term maintenance and risk-reduction. Conventional weight management with a 5–10 kg target can be effective, but should always use an evidence-based, structured, approach following clinical guidelines (4,29) based mainly on modifying food choices and incorporating physical activity when that becomes possible, with options for anti-obesity drugs where appropriate. This approach has been fully evaluated by the Counterweight Programme (30). It is highly cost-effective, on an Intention to Treat (ITT) basis, indeed *cost-saving* through long-term cost

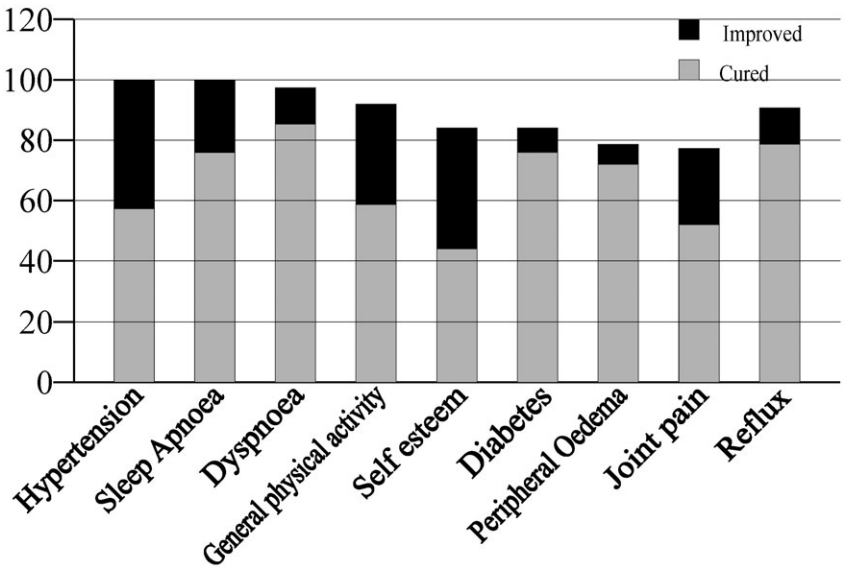

Figure 4 Multiple clinical benefits from weight loss 4 years after laparoscopic adjustable gastric banding (Frigg *et al.* (27)).

avoidance (31). However, the target of 5–10 kg loss at 1–2 years was achieved by only 30% of attenders, or one in six of all those who enter the programme. That is the reality of what can be achieved by 'all-comers' in routine primary care using the best available methods. Patients with T2DM tend to do less well, for a variety of reasons: metabolic rates tend to fall with improved diabetic control, hypoglycaemic drugs often cause weight gain, and these patients have usually already tried their best with diet and lifestyle.

If the real target for obese patients with T2DM is a maintained 15 kg weight loss, conventional diet and exercise programmes will not suffice. Only 2% of patients achieved this in the Counterweight audit. Using anti-obesity drugs together with a good diet and exercise programme has been shown to increase success rates in clinical trials, but still only about 5–10% of patients will maintain 15 kg loss with orlistat (32) or sibutramine (33). The main benefit for obese patients from anti-obesity drugs is from improved long-term weight maintenance, not just for weight loss. Patients find weight maintenance in our obesogenic environment more difficult than achieving weight loss. It has been difficult to assess the expected clinical impact of these drugs in routine clinical practice, because the published RCT results include substantial numbers of patients who do not respond to the drug, and who should be withdrawn from treatment at an early stage. Anti-obesity drugs do not benefit all patients equally, and should not be expected to.

The results of trials with all recently studied anti-obesity drugs show consistently that a mean weight loss of around 4–7 kg is maintained at 1–2 years (34) (Fig. 5) but studies which have used other methods to gain greater initial weight loss have demonstrated weight maintenance at a mean of about 10–12 kg below the baseline weight with sibutramine (35,36). Similarly with orlistat a mean weight

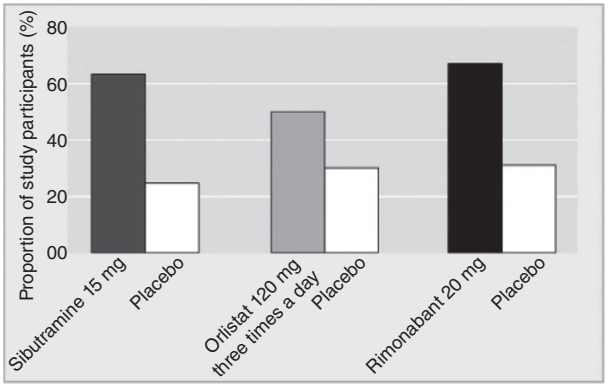

Figure 5 Proportion of study participants achieving 5–10% weight loss in 1 year, according to drug taken (data from combined datasets of 1 year phase 3 trials of three obesity drugs including rimonabant) (adapted from Finer N; Lean and Finer (34–35)).

loss 10–15 kg is seen for compliant, responding patients who achieve >4 kg loss at 3 months and then continue on treatment (32). A significant proportion of these patients managed to maintain >15 kg loss at 1–2 years. Results in obese patients with T2DM consistently show poorer weight loss. Most recently the data for liraglutide, has shown a mean weight loss of about 8 kg at 20 weeks (37) with further subsequent loss to 10–11 kg below baseline, maintained at 12 months in a RCT when it is given together with a good diet and exercise programme to non-diabetic patients with obesity (38). Liraglutide is licensed for diabetes treatment, and alone leads to modest weight loss maintained at about 3 kg below control groups (39) and does generate weight loss, but has not been studied formally together with a good diet and exercise weight-loss programme for obese T2DM patients, or in a realistic, routine clinic setting.

It has been shown many times that VLED can generate much more weight loss than conventional food-based diets, but weight regain has been a huge problem, preventing the recommendation of VLED in evidence-based guidelines. Meta-analysis of 80 non-surgical trials with 1-year follow-up found a mean initial weight loss of about 18 kg, which is approaching that achieved in some bariatric surgery series (40), e.g. mean 21 kg loss at 2 years following laparoscopic banding (15). However, weight regained rapidly to around 11 kg at 12 months and 8 kg at 2 year (40). This is in fact somewhat better than can be achieved by food-based diets and probably deserves re-evaluation by guideline-writers, but the regain is frustrating for both patients and treatment providers, and the numbers able to maintain weight loss >15 kg is still very small.

Given the proven value of anti-obesity medications for improving long-term weight maintenance, it is surprising that more studies have not combined VLED (for the weight loss phase) with full medical supporting treatment, including drugs where appropriate, for maintenance. The marketing, and indeed the regulatory processes for anti-obesity treatments, have almost exclusively focussed on the weight loss, to the disadvantage of patients whose greatest medical need is to improve weight maintenance.

There are several ways to enhance weight maintenance. The Counterweight studies demonstrated almost complete maintenance between 1 and 2 years, and in common with many other studies, showed that frequency of follow-up attendance and contact with healthcare professionals with some behavioural skills had the most important effect (30). A structured approach to the maintenance period is clearly important and has been neglected in the past. A recent Danish study has used a stepped food reintroduction programme to achieve good results (41). This type of approach has few costs and engages and empowers patients in the area they find most problematic.

Several trials have been published over the years, and all have shown substantial benefit in terms of long-term weight maintenance when a licensed anti-obesity drug was added to the effect of a VLED. Using dexfenfluramine (now no longer available) a mean weight loss of about 18 kg with VLED was increased to near 28 kg at 34 weeks (42). (Fig. 6a) A similar study by Andersen *et al*., however, showed no benefit for dexfenfluramine at 12 months, so not all maintenance programmes are equally effective (43). Using sibutramine, Apfelbaum *et al*. showed substantial additional effect following initial weight loss after VLED, with a maintained mean loss of 14 kg. Almost half these patients thus maintained >15 kg loss (44). (Fig. 6b) Importantly, these clinic based results have been replicate in a more realistic primary care setting, in the Netherlands, again showing a mean loss of 14 kg at 12 months, with sibutramine after VLED and further maintenance to 18 months (45). (Fig. 6c) A recent study using orlistat has produced very similar results, with weight loss maintained on a low-fat diet at about 14 kg below baseline at 12 months, 11 kg at 24 months and 9 kg at 36 months. A placebo-treated control group did less well, but still lost 7 kg at 3 years. Importantly the programme was very well accepted with 200 out of 309 completing 3 years (46). (Fig. 6d) A feasibility study is now well advanced in UK primary care, using 810 LCLD (Low Calorie Liquid Diet) with orlistat to complement the excellent weight maintenance diet and exercise methods developed by the Counterweight Programme. Early results show high levels of acceptability to both patients and primary care teams, and excellent early weight loss. There is a clear need to extend this work to T2DM patients.

Conclusions

The evidence reviewed here seems reasonably secure that the impressive short-term weight losses achieved with VLED can be maintained quite well using a combination of behavioural methods and anti-obesity medications, such that approaching 50% of patients might be expected to lose >15 kg, the amount which appears to reverse a diagnosis of T2DM. The results are not perfect and there is clearly scope for future research on improvements, particularly research based in realistic routine-care settings, and specifically obese T2DM patients.

For optimal weight loss there seems to be advantages in requiring patients to undertake a period on a purely synthetic liquid diet, including all essential micronutrients (LCLD). Including specific foods, to try to improve acceptability, impairs weight loss (47). The recent studies of Christensen *et al*. (41) and the Taiwan study (48) have shown very little difference in the weight loss effects of VLED (415 kcal day^{-1}) and a more liberal (810 kcal day^{-1} LCLD), so this seems the best approach to the weight loss phase under current evidence.

For long-term weight maintenance, behavioural methods are already effective, and can be improved and tailored to the needs of patients and to the skills of the supporting healthcare team. Although the best, and possibly most cost-effective, results are likely to arise from bariatric surgery, adding anti-obesity medication to behavioural approaches appears to generate results begin to challenge those from surgery. Orlistat is effective and the Glucagon-like Peptide-1 (GLP-1) agonists may prove even more so, with encouraging early results from liraglutide even without VLED (37,38).

Maintenance programmes without anti-obesity drugs or surgery such as that used in the Look AHEAD trial suggest better outcomes with high amounts of exercise, compliance with protocol and use of formula food product (49). Preliminary evidence from an RCT suggests that a highly motivated group (older people with knee osteoarthritis)

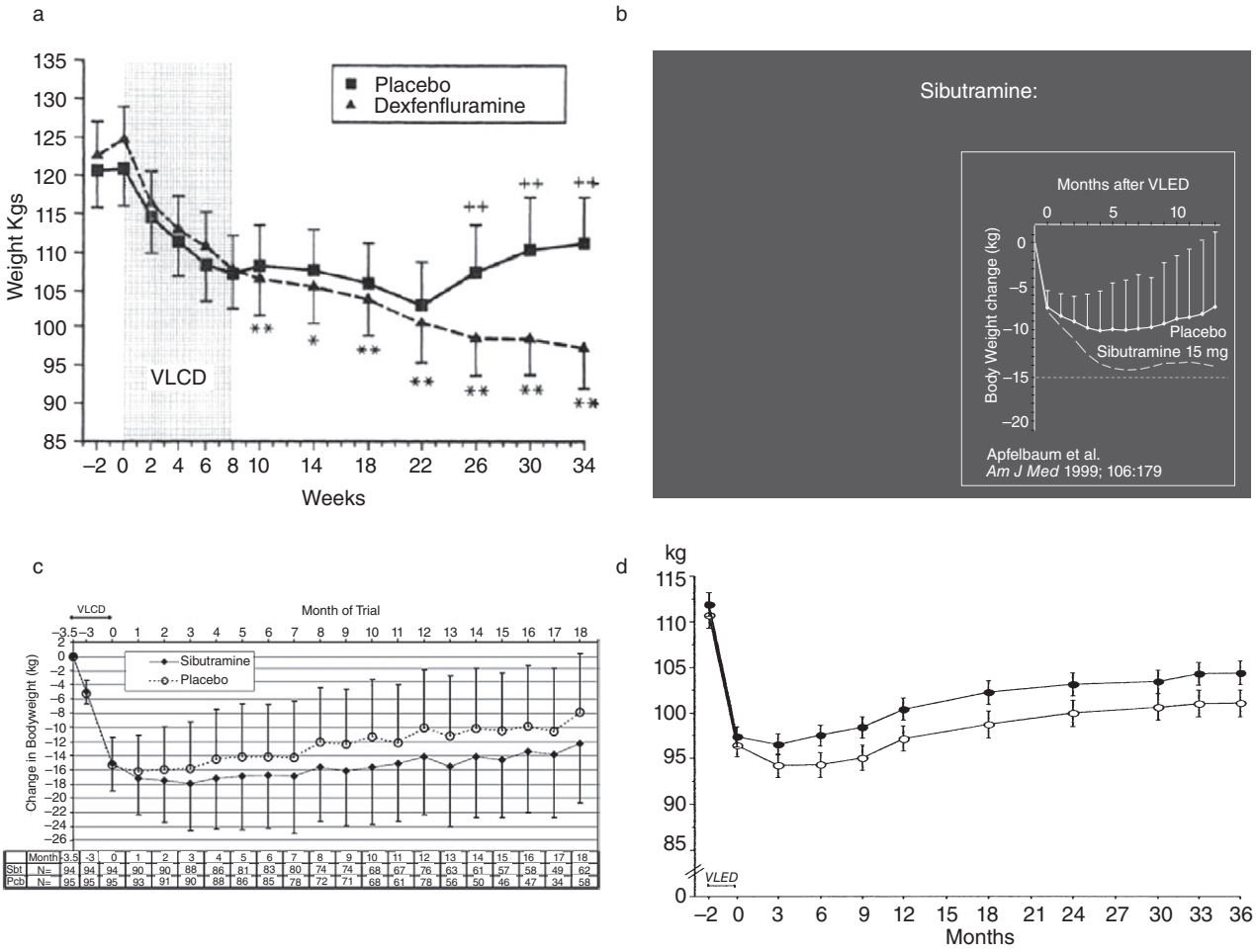

Figure 6 a. 330 kcal day^{-1} VLED followed by dexfenfluramine (Finer *et al.* (35)). b. Weight loss after very low-energy diet (VLED) – sibutramine (Apfelbaum *et al.* (44)). c. VLED with sibutramine for long-term maintenance in a GP setting (Mathus-Vliegen (45)). d. Body weight changes (Richelsen *et al.* (46)).

given intense management and regular part substitution of regular food with formula food product during maintenance can maintain on average more than 10 kg weight loss for 1 year with nearly half the patients maintaining major symptom improvement (50).

Waiting for the diagnosis of T2DM is not in patients' best interests. Providing more aggressive evidence-based weight management for all obese patients at an earlier stage may prove the most cost-effective strategy but T2DM will continue to be a major clinical problem. If the evidence discussed here is accepted to adopt new, potentially curative, approach to manage T2DM in routine care, this will have huge benefits for patients above those from the current mainly palliative management, which has only minor impact on the disastrous prognosis of T2DM. To allow this new focus on effective weight management, targeting >15 kg loss, there will be training needs and decisions will need to be taken to divert some of the funds currently absorbed by current guideline-driven management of T2DM and obesity and their complications. These decisions will need secure evidence on acceptability effectiveness and cost-effectiveness.

Conflict of Interest Statement

The author declares receipt of research funds, and funding to present at scientific meetings from Cambridge Weight Plan (Cambridge Manufacturing Ltd), and from Novo Nordisk.

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