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Very low-energy and low-energy formula diets: Effects on weight loss, obesity co-morbidities and type 2 diabetes remission – an update on the evidence for their use in clinical practice

A. Brown*,† and A. R. Leeds‡,§

*Centre for Obesity Research, University College London, London, UK;
†National Institute of Health Research, University College London Hospitals, London, UK;
‡Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark;
§Parker Institute, Frederiksberg Hospital, Copenhagen, Denmark

Abstract

The role of formula very low-energy diets (VLEDs, <800 kcal/day) and low-energy diets (LEDs, 800–1200 kcal/day) within clinical practice has regained attention over the last few years. Formula diets can achieve clinically significant weight reduction in the short-term (3–5 months) and new evidence demonstrates that long-term weight loss maintenance (up to 4 years) is achievable. Weight reductions of between 10% and 15% bodyweight have been reported, which is associated with clinically meaningful health outcomes in a number of obesity-related co-morbidities including type 2 diabetes (T2D), obstructive sleep apnoea and osteoarthritis. Recent evidence indicates that using a formula LED with a weight loss maintenance programme can help people with overweight or obesity and T2D achieve remission. Despite this, few healthcare professionals in the UK routinely use LEDs. Concerns about adherence, risk of precipitating eating disorders, safety, cost and long-term efficacy may, in part, contribute to their under use. To help inform healthcare professionals on the use of formula diets within clinical practice, this review examines the current evidence for the use of VLEDs and LEDs for weight loss and weight loss maintenance, and in the treatment of obesity-related co-morbidities, including T2D, osteoarthritis, psoriasis, obstructive sleep apnoea and secondary coronary prevention, with a particular focus on T2D remission.

Keywords: formula diets, low-calorie/energy diets, obesity, type 2 diabetes remission, very low-calorie/energy diets, weight loss

Correspondence: Dr. Adrian Brown, NIHR Research Fellow in Nutrition and Dietetics, Department of Medicine, Centre for Obesity Research, University College London, Rayne Building, 5 University Street, London WC1E 6JF, UK.
E-mail: a.c.brown@ucl.ac.uk

Introduction

Obesity represents one of the greatest public health challenges of modern times. In 2016, it was estimated that globally, 1.9 billion adults were overweight and 650 million were obese (World Health Organization

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2018b), representing an overall prevalence of approximately 12% (Afshin *et al.* 2017). Obesity can contribute to a greater risk of non-communicable diseases (NCDs) including type 2 diabetes (T2D), ischaemic heart disease, stroke and some cancers (Nyberg *et al.* 2018). With 71% of worldwide deaths attributed to NCDs (World Health Organization 2018a), effective treatment and management strategies for obesity and its co-morbidities, specifically T2D, are key priorities for healthcare systems worldwide.

Despite best efforts, the rising prevalence of obesity and obesity-related co-morbidities has not yet been adequately addressed with the tools currently available. In a systematic review of the effects of specialist Tier 3 weight management interventions for adults in the UK, weight reduction in the majority of studies ranged between 2 and 6 kg (Brown *et al.* 2017a,b). While a 5–10% bodyweight loss can have significant health benefits, weight loss of this magnitude has been suggested to be insufficient to give sustained and noticeable benefits in those with greater body mass indexes (BMI, ≥35 kg/m^2), which are often associated with serious medical conditions (SIGN 2010). Bariatric surgery remains the most effective treatment for severe obesity and its co-morbidities (Colquitt *et al.* 2014), with weight reduction of 20–30% being reported (Miras & le Roux 2013). However, not every patient wishes to have surgery, there is a risk of complications and access remains limited to <1% of eligible patients in the UK, far lower than other European countries and the US (Welbourn *et al.* 2016). As yet there is clearly an unmet need for cost-effective sustainable weight loss methods to address the burgeoning population of individuals with obesity and the tsunami of T2D that is about to overwhelm healthcare services worldwide.

Formula very low-energy diets (VLEDs) and low-energy diets (LEDs) are specially formulated food products, usually in the form of liquid soups, shakes and bars, and have been available in the UK for about 35 years (Leeds 2014). VLEDs provide fewer than 800 kcal/day (3347 kJ) and are designed to replace the whole diet using 3–4 products per day (NIH 1993; CODEX 1995; NICE 2014b); as such, they are defined as a total diet replacement (TDR). In comparison, a LED provides between 800 and 1200 kcal/day (3351–5021 kJ) and can either be a TDR or the formula products can be incorporated into modified conventional meals as a partial diet replacement. Typically, the TDR phase lasts 8–16 weeks within clinical trials (Johansson *et al.* 2014a; Leeds 2014; Lean *et al.* 2017), although this has been extended to 20 weeks to allow for greater weight reduction (Lean *et al.* 2017). The National Institute for Health and Care Excellence (NICE), however, recommends a maximum of 12 weeks of TDR at present (NICE 2014b), although there is a lack of evidence for this time limit.

There is now increasing interest in the use of VLEDs and LEDs in primary care and other therapeutic settings driven by increasing evidence for their efficacy and safety. Their capacity to facilitate weight reductions that lie in the void between those achieved through bariatric surgery and conventional diet interventions has been associated with clinically meaningful outcomes for a number of obesity-related co-morbidities (Garvey *et al.* 2016). Anxieties among healthcare professionals about the potential risks of rates of weight loss greater than 1 kg/week causing excessive lean tissue loss and rapid weight regain seem not to have been borne out in recent experimental work (Purcell *et al.* 2014; Christensen *et al.* 2017a,b). Greater rates of weight loss seem to be associated with better dietary compliance, possibly because rapid weight loss is highly motivating in some people and has been shown to be associated with increased weight maintenance (Wadden *et al.* 2011).

Formula VLEDs and LEDs have the potential to make a meaningful contribution to meeting the global challenge of obesity and its co-morbidities, the most prevalent of which is T2D. This review will examine the current evidence for the use of formula VLEDs and LEDs in weight loss and treatments of obesity-related co-morbidities, with particular focus on their use in T2D remission. The review is narrative in nature, with the intention of identifying and discussing relevant evidence within the area to help inform healthcare professionals on the use of formula diets within clinical practice. This is not a systematic review, rather, studies were examined and critically appraised to help clarify the current status of research within the area of formula VLEDs and LEDs.

Weight loss on very low-energy and low-energy formula diets

Formula VLEDs and LEDs have been shown to be effective at promoting significant weight loss in the short-term (up to 20 weeks) (Tsai & Wadden 2006; Christensen *et al.* 2011; Brown *et al.* 2015). During the TDR phase, individuals can typically lose between 10 and 16 kg or 10% and 15% of bodyweight (Johansson *et al.* 2014a; Leeds 2014; Lean *et al.* 2017), with initial weekly weight losses varying between 1 and 3 kg (Lean 2011; Leeds 2014; Brown *et al.* 2015). Weight loss has been shown to slow over time, possibly due to reduction in resting metabolic rate and reduced compliance to the formula diet (Hall *et al.* 2011; MacLean *et al.* 2015; Vink *et al.* 2016). Furthermore, there appears to be individual variability in the total weight loss achieved, with men and those with a higher initial bodyweight typically losing more weight (Lean 2011; Bischoff *et al.* 2012; MacLean *et al.* 2015).

In theory, due to the greater energy restriction, VLEDs should produce greater weight losses than LEDs. However, despite early studies showing greater weight reduction with VLEDs compared with LEDs in the short-term (Tsai & Wadden 2006), evidence indicates weight losses are comparable at 12 months, with the VLED group regaining 62% of the weight lost compared to 41% in the LED group (Tsai & Wadden 2006). A more recent controlled trial showed no difference in the extent of weight loss after 16 weeks of following either a VLED or a LED (Christensen *et al.* 2011).

Weight maintenance following very low-energy and low-energy formula diets

Weight maintenance remains the most challenging area of weight management in those with obesity. The exact mechanisms that drive weight regain following weight loss remain poorly understood but include physiological, psychological and biological factors. Weight regain following the initial TDR phase of formula VLEDs and LEDs is common without additional support. Often this occurs due to dropout from maintenance support, the rate of food reintroduction being too rapid, environmental factors or patients not addressing the reason for their initial weight gain.

Weight regain appears to be driven, in part, by underlying biological changes that make an individual feel hungrier and less satisfied after food, rather than simply a lack of will power. Following weight loss on a VLED, a compensatory increase in subjective hunger has been reported and associated with higher circulating levels of ghrelin (a hunger hormone) and lower circulating levels of peptide YY (PYY), leptin, amylin and cholecystokinin (satiety hormones) compared to baseline (Sumithran *et al.* 2011, 2013; Purcell *et al.* 2014). However, during the TDR phase of a VLED, evidence suggests that patients experience less hunger and greater satiety/fullness compared with baseline, despite the significant energy restriction (Sumithran *et al.* 2013; Gibson *et al.* 2014; Coutinho *et al.* 2017). This, in part, is believed to be related to patients being in a state of ketosis, which reduces hunger by lowering concentrations of circulating ghrelin (Sumithran *et al.* 2013). Emerging evidence suggests that these acute compensatory weight loss induced changes in gut hormones subside if the weight loss can be maintained (Iepsen *et al.* 2016), highlighting the importance of an effective weight loss maintenance programme after a formula diet.

Recent well-controlled studies suggest that weight loss maintenance is possible with the addition of several key strategies (Mulholland *et al.* 2012; Christensen *et al.* 2014, 2017b; Johansson *et al.* 2014a). For example, the continued use of formula products either daily (1–2 products per day) or intermittently (3 × 5-week periods each year) has been shown to aid weight maintenance for up to 4 years (Christensen *et al.* 2017b).

Pharmacotherapy has also been shown to have a positive effect on weight maintenance following a VLED (Johansson *et al.* 2014a) with Orlistat (a medication that prevents fat being absorbed from food) producing a 2.4 kg greater weight loss at 22 months compared with control. In another study of weight maintenance following a VLED, those given a GLP-1 receptor agonist continued to lose weight, required fewer meal replacement products to maintain their weight and had smaller decreases in leptin and higher PYY levels compared to those not on the GLP-1 receptor agonist (Iepsen *et al.* 2015).

Physical activity is often recommended to aid weight loss maintenance; however, following a VLED, evidence indicates that the beneficial effect of physical activity on weight maintenance is small (Fogelholm *et al.* 2000; Borg *et al.* 2002). However, physical activity may be beneficial in other ways. A recent systematic review of studies using either dual-energy X-ray absorptiometry (DEXA) or underwater weighing in those who achieved greater than 10 kg weight loss following a VLED showed that median lean tissue loss varied between 14% and 23.4%, depending on exercise levels (Webster *et al.* 1984; Saris 2001; Chaston *et al.* 2007). Both rigorous resistance and aerobic exercise have been shown to limit lean tissue loss after a VLED (Chaston *et al.* 2007; Snel *et al.* 2012a). Larger lean tissue loses have been seen in those with higher BMIs at baseline, possibly due to the larger energy deficit and insufficient dietary protein relative to body mass. This suggests that in those with a bodyweight greater than 135 kg, particular attention should be paid to the initial energy deficit achieved and protein intake (Nielsen *et al.* 2016). Several studies have reported that following the use of formula diets, the ratio of lean to fat mass loss is approximately 25:75 (Saris 2001); if the ratio is greater than this, reviewing protein intake and the rate of weight loss might be beneficial.

Weight management clinicians have traditionally suggested that losing weight in a slow and steady way is preferable for long-term weight maintenance as opposed to rapid weight loss, which is believed to result in rapid weight regain. However, evidence has recently emerged to suggest that this may not be the case (Purcell *et al.* 2014; Coutinho *et al.* 2017). In one study, individuals were supported to achieve a weight loss of ≥12.5% bodyweight, either 'rapidly', using a VLED for 12 weeks or 'slowly', using an energy deficit diet (400–500 kcal/day deficit) over 36 weeks, to assess the impact on weight regain (Purcell *et al.* 2014). Results indicated that the rate of weight loss had no effect on the amount or rate of weight regained over the subsequent 144 weeks. Furthermore, the amount of weight loss achieved by any means in the first year has been shown to be predictive of long-term weight loss maintenance (Astrup & Rossner 2000; Wadden *et al.* 2011; Rolland *et al.* 2014). This was evident in the *Look Action for Health in Diabetes* (*AHEAD*) study that showed those achieving ≥10% bodyweight loss (using a low-fat diet, meal replacements and exercise) at 1 year had a 10.4 times greater odds ratio of maintaining that loss at 4 years, compared to those that lost less than 5% in the first year (Wadden *et al.* 2011). The mechanisms driving this effect remain unclear but may relate to the motivation of actually losing significant weight.

The macronutrient composition of the diet after initial weight loss may also play a role in weight loss maintenance. This was assessed in a multicentre randomised trial, the *Diet, Obesity and Genes* (*Diogenes*) study (Larsen *et al.* 2011; Aller *et al.* 2014). Following a short 8-week weight loss phase using a LED (800–1000 kcal/day) to achieve at least 8% bodyweight loss, the study then assessed the effects of four different maintenance diets, which varied in protein content and glycaemic index (GI) (high-GI/high-protein; low-GI/high-protein; high-GI/low-protein; low-GI/low-protein). At 6 months, the low-GI/high-protein diet resulted in better weight loss maintenance than the other three maintenance diets; although at 12 months, only the protein content of the diet was found to positively influence weight maintenance (Larsen *et al.* 2011; Aller *et al.* 2014). This suggests that diets higher in protein may aid weight loss maintenance following a formula VLED or LED.

The gradual reintroduction of food following a LED or VLED is believed to assist with weight loss maintenance (Leeds 2014; Brown *et al.* 2015). For example, research has shown that reintroducing food over a 6-week period resulted in significantly less weight regain at 52 weeks compared with a reintroduction period of 1 week (3.9 kg vs. 8.2 kg, respectively) (Gripeteg *et al.* 2010). In addition, reintroducing food over 6 weeks was associated with increased dietary restraint (the tendency to eat less than desired) and reduced external eating (the tendency to eat in response to external cues such as the sight of food) compared to reintroduction lasting only 1 week. It is possible that the use of a partial formula diet during the reintroduction phase will also enable individuals to feel more in control of their food intake. Although this is an area in need of further research, the food reintroduction phase is believed to be an important driver of weight loss maintenance following the TDR phase (Lean *et al.* 2017).

Finally, the use of behaviour change techniques has been shown to support weight maintenance following a formula diet (Mulholland *et al.* 2012; Parretti *et al.* 2016). A recent systematic review compared changes in weight loss using a behavioural programme alone and a VLED plus behaviour change such as self-monitoring, planning ahead, goals setting and removing food cues. At 1 year, the VLEDs combined with a behavioural programme achieved a 3.9 kg greater weight loss than the behavioural programme alone (Parretti *et al.* 2016). Table 1 summarises the weight loss, glycaemic control, surrogate markers of cardiovascular risk and attrition of the formula VLEDs and LEDs.

Type 2 diabetes and very low-energy and low-energy diets

Weight loss and type 2 diabetes

Weight loss remains the primary nutritional management strategy for adults with overweight or obesity and T2D (Dyson *et al.* 2018), with weight losses of greater than 5% bodyweight leading to improvements in glycaemia, blood lipids, insulin sensitivity and blood pressure (Albu *et al.* 2010; Franz *et al.* 2015). Intensive multicomponent lifestyle interventions consisting of energy restriction, physical activity and behaviour change, alongside patient education, remain the cornerstone in the management of patients with both obesity and T2D (Brown *et al.* 2017a) and have been used to promote weight loss in people with T2D

Table 1 Summary of outcomes from formula very low-energy diets (VLEDs) and low-energy diets (LEDs)

Weight loss strategies	Follow-up (months)	Weight loss (kg)	HbA1c (%)	Fasting blood glucose (mmol/l)	Blood pressure (mmHg) SBP	DBP	Lipids (mmol/mol) T. Chol	LDL-C	TG	Waist circumference (cm)	Attrition (%)
VLED + TDR*	1 to 4	12.4 to 27.2	−1.1 to −1.5	−4.3 to −4.4	−11.1 to −21	−5 to −9	−0.73 to −1.3	−0.49 to −0.7	−0.06 to −1.3	−8.6 to −25	4 to 10
VLED + Maintenance phase	2 to 33	4.1 to 15.4	−0.2 to −3.8	−0.3 to −4.3	−16 to 1	−9 to 1	−0.02 to −1.1	−0.11 to −0.7	−0.06 to −0.82	−7 to −12.8	4 to 41
LED + TDR†	1 to 4	7.9 to 16.9	N/A	−0.43	−2.6 to −11.7	−4.4 to −6.9	−0.84	−0.51	−0.13	−8.1 to −13.1	7 to 17
LED + Maintenance phase	4 to 48	9.9 to 12.4	−0.17 to −1.3	−0.18 to −2.4	−1.3 to −7.8	−2.4 to −9.4	−1.02 to 0.04	−0.01 to −0.72	−0.13 to −0.88	−8.9 to −11.3	0 to 52

DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T. Chol, total cholesterol; TG, triglycerides.

This table summarises the effect of VLED and LED on weight reduction, glycaemic control, surrogate markers of cardiovascular disease and attrition. Data are presented from the total diet replacement (TDR) phase and also the maintenance phase for both VLEDs and LEDs.

*Sources of the data on VLEDs: Wing *et al.* (1991, 1994), Kajaste *et al.* (2004), Tsai and Wadden (2006), Hammer *et al.* (2008), Tuomilehto *et al.* (2009), Johansson *et al.* (2009), Christensen *et al.* (2011), Johansson *et al.* (2011), Snel *et al.* (2011), Lim *et al.* (2011), Snel *et al.* (2012a,b,c), Sumithran *et al.* (2011), Sumithran *et al.* (2013), Johansson *et al.* (2014a); Purcell *et al.* (2014), Steven and Taylor (2015) and Steven *et al.* (2016a,b).

†Sources of the data on LEDs: Wing *et al.* (1994), Christensen *et al.* (2011), Lean *et al.* (2013), Christensen *et al.* (2013), Pedersen *et al.* (2015); Jensen *et al.* (2013), Atukorala *et al.* (2016), Lean *et al.* (2017), Christensen *et al.* (2017a,b, 2018), McCombie *et al.* (2018), and Astbury *et al.* (2018).

(Franz *et al.* 2015; Terranova *et al.* 2015). When compared with standardised diabetes care in those with T2D, using an intensive multicomponent lifestyle intervention that included meal replacements, a low-fat diet and physical activity has been found to produce greater weight loss, improvements in glycaemia and T2D remission (Gregg *et al.* 2012; Esposito *et al.* 2014). There remains uncertainty regarding the most effective dietary intervention to foster weight loss (Nield *et al.* 2007), but what is key is choosing a lifestyle change a patient is willing to stick to in the long-term (Johnston *et al.* 2014).

The use of formula diets for those with T2D is not a new practice. Prior to the recent resurgence in this dietary approach, studies have shown formula diets to be beneficial in this patient group. In a study on a metabolic ward where patients with or without T2D were provided with a VLED for 36 days, those with T2D showed rapid improvements in glycaemic indices and both groups showed normalisation of triglycerides and total cholesterol, although those without T2D lost more weight over this period (Henry *et al.* 1986). In another study of patients with obesity and T2D, a standard behavioural therapy programme was compared with behavioural therapy plus an 8-week VLED TDR phase. The use of a VLED plus behavioural therapy produced a greater reduction in both fasting blood glucose and glycated haemoglobin (HbA1c) levels than the behavioural therapy alone, although the groups did not differ in terms of weight loss (Wing *et al.* 1991), a finding that was replicated in those without T2D (Wadden & Stunkard 1986). Finally, the intermittent use of a VLED in patients with T2D and obesity (2 × 12-week periods of 400–500 kcal/day) produced greater weight loss than a food-based LED (1000–1200 kcal/day), although fasting blood glucose and HbA1c levels did not differ between the groups; however, those who lost the most weight had the greatest improvement in their HbA1c levels (Wing *et al.* 1994).

Weight loss and type 2 diabetes remission

The idea that T2D can be put into remission using dietary methods is not new. In an ancillary analysis of the *Look AHEAD* cohort, subjects in the intensive multicomponent lifestyle intervention group were more likely to experience T2D remission (11.5%, partial or complete) compared with those who received standardised care (2%). However, rates of remission declined over the follow-up period, with only 7% remaining in remission at 4 years in the intensive multicomponent lifestyle intervention group compared with none in the standard care group (Gregg *et al.* 2012). In another study (Esposito *et al.* 2014) that compared a low-carbohydrate Mediterranean diet to a low-fat diet, T2D remission was reported in 14.7% at 1 year in the low-carbohydrate Mediterranean diet group compared with 4.1% in the low-fat diet group (Esposito *et al.* 2014). More recently, a non-randomised, controlled study using a novel remote care model, which included a well-formulated ketogenic diet compared with usual care, showed the ketogenic diet achieved T2D remission in 25% of participants compared with no cases in the usual care group (Hallberg *et al.* 2018). Similar to the results of the *Look AHEAD* trial, remission rates reduced over time in both studies (Esposito *et al.* 2014; Hallberg *et al.* 2018).

Evidence suggests that there is a need for 15 kg weight loss to induce T2D remission in those with recently diagnosed T2D (Dixon *et al.* 2008; Lean 2011; Lean *et al.* 2017). However, weight loss interventions in patients with obesity and T2D typically achieve only 2.4–8.5 kg reduction in bodyweight, even in clinical trials (Franz *et al.* 2015). This raises the question of whether current standard care is able to produce the weight loss required to bring about T2D remission in a significant number of patients. Bariatric surgery remains the most effective treatment for both obesity and T2D (Colquitt *et al.* 2014). Weight losses of between 20% and 35% of bodyweight have been reported 2 years after bariatric surgery (Miras & le Roux 2013), with between 30% and 60% of patients achieving T2D remission (Rubino *et al.* 2017). These figures, however, vary with operation type and weight loss and glycaemic control deteriorates over time in a substantive number of patients (Yu *et al.* 2015; Schauer *et al.* 2017). The exact mechanisms which drive improvements in, and remission of, T2D following bariatric surgery remain to be fully understood, although are hypothesised to include alterations in gut hormones, bile acid changes, adaptions in the microbiome and changes in food preferences and smell (Miras & le Roux 2013; Batterham & Cummings 2016). Recent evidence points towards the acute energy restriction that occurs immediately following bariatric surgery playing a pivotal role in the early glycaemic improvements seen in both biliopancreatic diversion (BPD) and Roux-en-Y gastric bypass (RYGB) (Jackness *et al.* 2013; Lips *et al.* 2014), which occurs prior to any changes in bodyweight or alterations in plasma GLP-1 levels (Steven *et al.* 2016b). With only a fraction of individuals accessing surgery, there is a need for other treatment options to help achieve clinically relevant weight loss that may bring about T2D remission. Formula VLEDs and LEDs are considered to have great potential to fill this gap (Brown *et al.* 2015).

Type 2 diabetes remission using formula diets

The Twin Cycle hypothesis was first reported in 2008 and proposed that fat deposition, specifically within the pancreas and liver, was key to the aetiology of T2D (Taylor 2008). It is postulated that a positive energy balance causes infiltration of fat into the hepatocytes and pancreatic islet cells, which, in turn, drives two corresponding metabolic cycles, causing a reduction in hepatic insulin sensitivity and suppression of first phase insulin response (initial release of insulin following nutrient ingestion), respectively (Lim *et al.* 2011), resulting in the development of T2D. The idea of fat infiltrating the pancreatic beta cells is not new, with first descriptions over 20 years ago in rat models of T2D (Lee *et al.* 1994; Unger 1995). Within this model, pancreatic fat was assessed and it was shown that the peak accumulation of fat in the pancreatic islet cells corresponded with the development of hyperglycaemia, reduction in insulin secretion and development of overt T2D (Lee *et al.* 2010). This suggested that assessing fat in the human pancreas may help predict risk of T2D; however, due to difficulties with non-invasive quantification of fat in human islets cells, this has not been possible to assess until relatively recently (Tushuizen *et al.* 2007; Lingvay *et al.* 2009; Lim *et al.* 2011).

The first study to assess the Twin Cycle theory in humans was the *COUNTER acting Pancreatic inhibition of Insulin secretion by Triglycerides* (*Counterpoint*) proof-of-concept study, which involved 11 patients with obesity and recently diagnosed T2D (<4 years) following a VLED for 8 weeks. After completing the diet, their fasting blood glucose was normalised (<7 mmol/l), in addition there was a normalisation of hepatic insulin sensitivity and return of first phase insulin compared to age- and weight-matched controls (Lim *et al.* 2011). These improvements corresponded with a reduction in liver and pancreatic triacylglycerol levels. Although this is not considered full T2D remission, it showed for the first time that acute energy restriction using a formula VLED influenced two key features of T2D.

This proof-of-concept study was proceeded by the *Counteracting BetA cell failure by Long-term Action to Normalise Calorie intake* (*Counterbalance*) study on 30 subjects from the same group with either short duration (<4 years) or longer duration of T2D (>8 years). This study aimed to assess whether normalisation of fasting plasma glucose (<7 mmol/l) following a VLED was maintained during weight stability at 6 months. In those with T2D for more than 8 years, only 50% achieved a fasting plasma glucose of <7.0 mmol/l at 8 weeks, without any other anti-diabetic medication, compared with 87% in those with T2D duration of <4 years (Steven & Taylor 2015). Despite this difference, significant improvements were reported in general health, blood pressure and lipid profile in all participants. The second paper from the *Counterbalance* study demonstrated that after the VLED and once patients had returned to an isocaloric diet, normalisation of fasting plasma glucose was maintained for 6 months in 12 subjects (40%), who were defined as 'responders' (Steven & Taylor 2015; Steven *et al.* 2016a). The responders had lower HbA1c/fasting glucose and higher plasma insulin levels, were younger, had a lower body mass, shorter T2D duration, were on fewer medications and, importantly, had lower levels of pancreatic fat (Steven *et al.* 2016a). Although these data suggested that T2D could be put into remission with acute energy restriction, due to methodological weaknesses that included lack of controls, selection bias and small participant numbers, more studies were required to inform clinical practice.

Many of the questions posed within these initial studies have now been addressed with the recently published *Diabetes in Remission Clinical Trial* (*DiRECT*) (Lean *et al.* 2017). This trial was designed to answer whether or not using a formula LED, followed by a long-term programme of weight loss maintenance in primary care, would result in remission of T2D in those diagnosed with T2D in the previous 6 years, and if a 15 kg weight loss was possible in primary care (Lean *et al.* 2017). T2D remission, defined as having an HbA1c <6.5% (48 mmol/mol) and off all diabetes medication for at least 2 months from baseline to 12 months, and 15 kg weight loss were the primary end points.

In this randomised control trial (RCT), 306 participants with T2D were recruited from 49 general practices and randomised to either best practice NHS care alone (control group) or best practice NHS care plus an intensive structured weight management programme (intervention group, Counterweight-Plus weight management programme). The intervention group received a formula LED TDR (825–853 kcal/day) for 3–5 months, depending on weight loss, followed by stepped food reintroduction (2–8 weeks) and then a structured weight loss maintenance programme. At 12 months, in an intention to treat analysis, 46% of participants achieved T2D remission in the intervention group compared to 4% in the control group. In addition, 24% achieved ≥15 kg weight loss in the intervention group compared to none in the control group, with overall mean weight reduction of 10 kg in the intervention group and only 1 kg in the control group. Interestingly, increased weight loss was associated with a higher rate of T2D remission: 73% of those achieving ≥10 kg weight loss went in T2D remission, while 86% of those with ≥15 kg weight loss achieved remission. This study clearly showed that T2D remission could be achieved for a large percentage of people with T2D within a primary care setting and should be considered a goal of treatment in those with recently diagnosed T2D (Diabetes UK 2018).

A subgroup of patients from the *DiRECT* study were assessed to explore pathophysiological differences between those that did (responders) and did not (non-responders) achieve T2D remission (Taylor *et al.* 2018). The results showed that the early and sustained improvement in beta cell function and the ability to recover first phase insulin response as key to T2D remission (Taylor *et al.* 2018). In addition, responders had shorter duration of T2D, lower HbA1c levels, higher fasting plasma insulin levels and higher plasma alanine aminotransferase levels than non-responders.

The use of formula diets in those patients with T2D and treated with insulin is less well studied and the benefits not yet fully established. Studies in this cohort have focussed on the use of formula VLEDs and have shown significant improvements in weight loss, low-grade inflammatory markers, body composition, surrogate markers of CVD including blood pressure, plasma lipids, quality of life and glycaemic control (Christiansen *et al.* 2000; Jazet *et al.* 2005, 2007, 2008; Snel *et al.* 2011, 2012a,b,c). However, it should be noted that these studies lacked control groups (that did not include a VLED) and included only small numbers of subjects in whom all diabetes medication including insulin was ceased, which indicates that the subjects had residual pancreatic function, something that not all advanced T2D patients will have, therefore questioning the validity and transferability of the findings. Despite these methodological issues, these studies hint that using a formula VLED may be of benefit within this patient group, although high quality research is needed to confirm these findings.

Despite the recent resurgence of research on formula diets and T2D within clinical practice, questions remain regarding how best to pragmatically translate the research findings into current healthcare practices. With limited healthcare resources available to manage and treat those with T2D and obesity, offering a formula VLED or LED to all may not be financially viable. A targeted, individualised approach may be more feasible, but future research is necessary to identify those individuals with T2D that are most likely to respond positively to a formula diet.

The management of medication is an important consideration and should be appropriately managed by an individual's medical team both during and following formula diets. Oral hyperglycaemic medications (sulphonylureas) and insulin requirements require significant reductions to reduce the risk of hypoglycaemia, with the suggestion of a pre-emptive reduction of insulin by 25% at the commencement of a VLED (Haslam *et al.* 2010). Anti-hypertensive medication should also be reviewed to avoid low blood pressure, which is a common side effect in those using formula VLEDs or LEDs. Protocols for managing T2D and blood pressure medications when using a formula diet are published in the *DiRECT* study protocol and the *Doctor Referral of Overweight People to Low-Energy total diet replacement Treatment* (*DROPLET)* study paper (Leslie *et al.* 2016; Astbury *et al.* 2018). Furthermore, it is essential that patients that do achieve T2D remission should continue to be monitored for T2D-related complications and also deterioration of glycaemic control at least annually (Diabetes UK 2018).

The cost-effectiveness of formula diets for treatment of T2D and whether they are a viable option within clinical practice are important considerations. A recent cost analysis of the intervention used in the *DiRECT* trial showed the total cost per intervention participant was £1223, with formula products and practitioner visits making up the majority of costs (95%) (Xin *et al.* 2018). It was estimated that each case of T2D remission would cost on average £2564 compared with £846 per participant in the control group receiving standard NHS care. It is clear from this analysis that the *DiRECT* intervention is more expensive to deliver than standard care, but when compared with the cost of the *Look AHEAD* intervention (US$2865 per participant) (Rushing *et al.* 2017) and bariatric surgery, which is estimated to have a mean cost of US$14 389 per participant (Doble *et al.* 2017), this is clearly an attractive option.

Formula diets in the management of other obesity-related co-morbidities

Osteoarthritis

With ageing populations that are heavier than in the past, the prevalence of osteoarthritis (OA) is increasing (Cross *et al.* 2014). There is currently no medication or other intervention proven to slow the disease process. Treatment is palliative until surgical joint replacement, total or partial, becomes necessary. Weight reduction is a core feature of osteoarthritis guidelines (NICE 2014a) but is difficult to achieve in those with limited mobility and who may have disturbed sleep (due to pain) and depression.

Early studies suggested a role for TDR as therapy for OA (Aaboe *et al.* 2011; Bliddal *et al.* 2011) and were followed soon afterwards by a definitive clinical trial at the Parker Arthritis Institute in Copenhagen. The two phase *Cartilage and Osteoarthritis weight loss trial* (*CarOT*) recruited obese people with knee OA for an initial comparison of weight loss with 8 weeks on either a VLED (415 kcal/day) or a LED (810 kcal/day) followed by stepped food reintroduction up to 1200 kcal/day by 16 weeks (Christensen *et al.* 2011, 2014, 2017b). The same participants then entered the second phase of the *CarOT* which was an RCT of weight loss maintenance for 12 months comparing three groups: (1) one meal replacement product daily with conventional food; (2) leg muscle strengthening exercises with conventional dietary restriction; and (3) control (no intervention).

All participants in the *CarOT* were then invited to enter a third RCT: the 'long-term intervention with weight loss in patients with concomitant obesity and knee OA' (*LIGHT*) trial, a 3-year RCT comparing one meal replacement product daily with intermittent use of an 810 kcal/day TDR for 5 weeks every 4 months. One hundred and ninety-two patients (average weight 103 kg, BMI 37 kg/m^2) entered phase one: average weight loss at the end of the 16-week period was 12 kg after the LED and 13 kg after the VLED. (Christensen *et al.* 2011). After 1 year of the second phase maintenance intervention, the diet group (one meal replacement product/day) maintained 11 kg weight loss on average, the exercise group 6 kg and the control group 8 kg (Christensen *et al.* 2014). Osteoarthritis symptom scores were significantly improved (less pain) after the initial weight loss and after 1-year maintenance (no difference between the groups). Lean mass losses at 1 year were between 9% and 13%, lower than expected possibly due to increased activity. Biomechanics studies on the same subjects showed that each 1 kg weight reduction reduced the peak knee load by 2.2 kg (Aaboe *et al.* 2011). Both interventions used in the *LIGHT* 3-year maintenance study resulted in maintenance of the initial weight loss of 10% achieved in the *CarOT* in 108 out of 153 participants who managed to complete the full 3-year study, with no significant differences between the groups (Christensen *et al.* 2017b). Furthermore, reduction of symptom scores and reduced blood pressure were maintained, demonstrating the effectiveness of such a programme on OA. Imaging studies on subsets of these participants in the *CarOT* and *LIGHT* studies showed that inflammation in the Hoffa's fat pad (under the patella) (Ballegaard *et al.* 2014) and synovial membrane (Riis *et al.* 2016) was related to the severity of knee pain, suggesting that reduction of inflammation associated with weight loss is the mechanism that results in pain reduction.

A large-scale observational study undertaken in Australia on 1383 people (average BMI 34 kg/m^2) with knee OA explored the effects of an 18-week healthy weight loss programme and allowed a threshold for symptomatic benefit to be established: participants needed to achieve more than 7.7% bodyweight loss in order to achieve clinically important symptom improvement in symptoms of knee OA (Atukorala *et al.* 2016). Just over half the participants achieved at least 7.7% weight loss. There was an option to use two meal replacement products daily in the first 6 weeks but the weight loss programme was otherwise based on conventional foods. In the study by Christensen *et al.* (2011), following 8 weeks of TDR, the initial weight loss of 12% resulted in rapid knee OA symptom improvement (good responses in >60% of participants). Participants were highly motivated to continue the diet by the reduction of pain. Compliance was impressive (dropout rate was 14 out of 192, about 7%) and more than 50% managed to maintain around 10% weight loss with symptom improvement for 4 years. Weight loss and subsequent maintenance is a surrogate marker for dietary energy intake and energy expenditure, a sustained change of which drives reduction of pro-inflammatory and pro-insulin resistance signalling (Geyer *et al.* 2016). This was demonstrated in a study of 43 healthy participants with obesity to assess the effect of a TDR on blood proteins (Geyer *et al.* 2016). Following the initial TDR, there was a 12% weight loss, which was tightly maintained at 12 months. Ten out of 400 proteins associated with the pro-inflammatory state showed a prompt reduction during the initial weight loss and then continued to fall throughout the 12-month weight maintenance period. Four proteins associated with insulin resistance also fell promptly and remained low throughout the year.

There would seem to be few contraindications to rolling out an effective intensive lifestyle intervention for the millions of people with knee OA whose quality of life is seriously impaired by pain, poor sleep and immobility when evidence indicates that TDR is an effective treatment for knee OA in a high proportion of those with this condition. That this has not been done might reflect healthcare practitioners' lack of experience with using TDR, long-held myths about adverse effects of TDR and innate conservatism and resistance to change in medical practice. Nevertheless, further investigation is needed into the reasons, beyond dietary compliance, why some people with knee OA respond better than others to TDR (disease stage and variation in 'metabolic burden' are likely influences on symptom response). The evidence on weight loss in knee OA should not be extrapolated to OA in other joints, but anecdotal evidence hints that weight loss may improve stiffness and reduce pain in hand OA. A randomised trial of weight loss with TDR in hand OA is about to start at the Parker Institute in Copenhagen.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) increases risk of stroke and myocardial infarction through raised blood pressure and blood pressure fluctuations, among other variables. OSA is associated with obesity in some people and represents an additional problem for many people with T2D. As a previously neglected obesity co-morbidity, OSA is now identified more commonly and is treated with continuous positive airways pressure or similar devices.

The evidence for a beneficial effect of weight loss among OSA patients has long been recognised in Scandinavia but even after publication of two high-quality studies (Johansson *et al.* 2009, 2011), little has changed in the use of weight reduction for OSA management in the UK, again perhaps reflecting healthcare practitioners' lack of experience with using TDR. The first of these studies (Johansson *et al.* 2009) was in 63 men with moderate or severe OSA who were randomised to control (no treatment) or a VLED (550 kcal/day) over 9 weeks. Those in the VLED group showed an average weight loss of 18.7 kg with 26 out of 30 demonstrating improved OSA scores (five were 'cured' of their OSA), in comparison to the control group who showed an average weight gain of 1 kg with mostly unchanged symptoms of OSA, though 5 out of 33 did show improvements.

Johansson *et al.* (2011) then offered the control group the same VLED programme and followed all 63 participants for 1 year at which point 30 out of 63 no longer required continuous positive airways pressure, with six of them being in full OSA remission. Those who completed the full programme maintained 17 kg weight loss, while weight maintenance was 12 kg on a basal observation carried forward basis over 1 year. Interestingly, those who lost most weight or who had the most severe OSA at baseline gained the most benefit from this intervention (Johansson *et al.* 2011).

Several other studies have also showed that using VLEDs or LEDs in patients with obesity results in clinically relevant improvement in weight loss, Apnoea/Hypopnoea Index (AHI), oxygen desaturation index and resolution of OSA, with reduction of AHI equating to less than five events/hour (Kajaste *et al.* 2004; Tuomilehto *et al.* 2009; Nerfeldt *et al.* 2010).

Cardiovascular and cardiac rehabilitation

Data from systematic reviews (Mulholland *et al.* 2012; Parretti *et al.* 2016) have suggested that the use of formula VLEDs might reduce CVD risk with improvements seen with surrogate CVD risk markers including blood pressure, lipid profile and glycaemic control.

One pilot study (Olsen *et al.* 2015) compared TDR with exercise training (aerobic interval training) on coronary microvascular function in women with coronary artery disease and showed that both interventions significantly improved microvascular function. The findings suggested that achieving an initial bodyweight loss of 10% followed by a weight maintenance programme with aerobic interval training gave superior outcomes at 1 year compared to aerobic interval training followed by dietary guidance with continued aerobic interval training. The initial weight reduction with TDR was associated with increased insulin sensitivity (Pedersen *et al.* 2015), a less atherogenic blood lipid profile (Pedersen *et al.* 2016), a relatively small loss of lean mass, and improved cardiovascular fitness compared to the initial aerobic interval training programme followed by aerobic interval training and dietary advice. Larger weight losses are not a standard component of cardiac rehabilitation and further large-scale trials are needed to determine whether weight loss with TDR should be a component of cardiac rehabilitation. A further trial has been designed.

Psoriasis

Most inflammatory changes are invisible, though may be marked by symptoms such as pain and stiffness. In psoriasis, an autoimmune disease characterised by patches of red, thickened and scaly skin, the extent and severity of inflammatory change in the skin can be assessed by clinical examination. With evidence showing marked improvement in inflammation following a VLED (Geyer *et al.* 2016), it is possible that this approach may help with psoriasis symptoms. A pilot RCT by Jensen *et al.* (2013) followed by a 1-year observational period showed that average weight loss of 15 kg in people with psoriasis could be achieved with a VLED TDR and about two-thirds of that weight loss was maintained for a year. The skin scores improved in a clinically meaningful way, and those improvements were largely maintained in those who stayed in the programme (Jensen *et al.* 2016). Though only a pilot trial, this work was recognised as a landmark contribution to psoriasis management for which effective diet, weight and lifestyle management interventions are lacking. In view of the complex interplay of genetic, environmental and psychological factors in psoriasis (Jensen & Skov 2016), it was unforeseen that weight loss alone would deliver such a dramatic effect (though the epidemiology of psoriasis does show a clear effect of bodyweight on disease risk) and these preliminary findings should be followed by a multicentre large-scale clinical trial. People with OA and psoriasis have adverse cardiovascular risk profiles and both the weight loss studies in psoriasis (Jensen *et al.* 2014) and OA (Christensen *et al.* 2013) showed improvements in cardiovascular risk factors.

Use of formula very low-energy and low-energy diets in primary care settings

Clinical trial evidence for the efficacy of formula diet programmes has largely been gathered in research settings in major institutions or primary healthcare settings. Global demand for weight loss exceeds the capacity for secondary healthcare services to deliver formula diets, therefore offering them in primary care is a potential solution. In the *DROPLET* pragmatic RCT (Astbury *et al.* 2018), 278 participants were recruited from GP practices. They were randomised to either a LED TDR (810 kcal/day) for 8 weeks followed by 4 weeks of food re-introduction and then a 12-week weight loss maintenance programme delivered by a commercial counsellor in the community, or to usual care provided by local practice nurses. At

12 months, the LED TDR group lost on average 10.7 kg (10% bodyweight) compared with 3.1 kg in the control group (see Fig. 1). Almost half (45%) of people in the LED TDR group achieved ≥10% weight loss compared to 15% in the control group. The greater weight loss achieved and maintained following TDR was associated with significantly greater improvements in levels of HbA1c, fasting blood glucose, and blood triglycerides, and insulin sensitivity and quality of life compared to usual care. When contact with the counsellor was reduced, patients regained weight, which is not unique to formula diets. This highlights the importance of a structured weight loss maintenance programme to minimise weight regain. Prescribing challenges related to reduction of medication dosage were well met by GPs with the help of medication protocols (Primary Care Sciences Oxford 2018). The study by Asbury *et al.* concluded that a TDR programme is an acceptable, safe and effective treatment for obesity in primary care and demonstrated that an alternative, scalable model of delivery for a formula TDR programme was possible. A full health economics analysis will be published but a preliminary account indicated that TDR is cost-effective by usual NICE standards (£20 000 per quality-adjusted life year) (Kent *et al.* 2018).

Other studies that have looked at the application of formula LEDs in primary care for obesity treatment are the two service evaluations of the 'Counterweight-Plus' programme (Lean *et al.* 2013; McCombie *et al.* 2018). In the initial feasibility study, at 12 months, 68 of the initial 91 patients achieved a mean weight loss of 12.4 kg with 33% achieving ≥15 kg weight loss at 12 months. Following this study, the full Counterweight-Plus programme was commissioned and recent 4-year audit data have been published (McCombie *et al.* 2018). Two hundred and eighty-eight patients commenced the programme. At 12 months, in an intention to treat analysis, subjects had achieved a mean weight loss of 10.5 kg, with 22.1% achieving ≥15 kg weight loss and 31.8% achieving >10 kg weight loss. Weight loss at 3 and 6 months was positively correlated to weight loss at 12 months, showing that helping subjects achieve a high initial weight loss may benefit long-term maintenance. Attrition within this evaluation was 44.2%, slightly higher than that reported in previous studies using formula diets but typical of the follow-up rate found in clinical practice (Brown *et al.* 2017b). Despite some limitations in these service evaluations studies, including the lack of randomisation, possible selection bias, and significant dropout, taken with the *DROPLET* study findings, they show that for motivated patients a formula LED approach combined with a weight loss maintenance programme can achieve clinically significant weight loss in primary care.

Nutritional issues with formula diets

Questions still remain about the possible detrimental effects of formula diets on vitamin and mineral status, particularly during the weight loss phase and in those

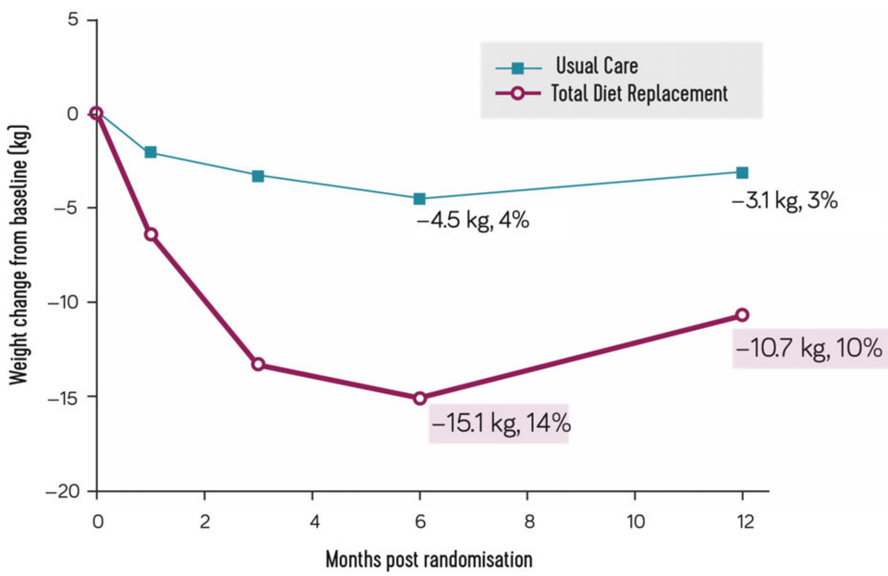

Figure 1 Estimated weight change over 12 months in the intention to treat population of the DROPLET trial. Weight loss shown in kg and as percentage of bodyweight. Figure redrawn from Astbury *et al.* (2018) with permission. [Colour figure can be viewed at wileyonlinelibrary.com]

with a higher BMI (Damms-Machado *et al.* 2012; EFSA NDA Panel 2015). However, in studies assessing micronutrient quality in popular energy-restricted diets including the South Beach, Atkins and Dietary Approaches to Stop Hypertension (DASH) diets, it was shown that these fail to meet US Reference Daily Intake (RDI) for many and, in the case of some diets, all micronutrients analysed (Calton 2010; Gardner *et al.* 2010). As three to four formula TDR products per day provide 100% of the Population Reference Intakes (PRI) for minerals and vitamins, this approach may well provide a more balanced micronutrient supply than conventional weight loss diets.

Data on micronutrient status of those following a formula diet are limited. One study demonstrated that a formula LED resulted in no change in ferritin levels, an increase in vitamins D and B_{12} levels and a decrease in parathyroid hormone (reflecting reduced secondary hyperparathyroidism caused by vitamin D deficiency) (Christensen *et al.* 2013). However, another study suggested that the vitamins and minerals provided in a formula LED were insufficient to meet demands of an obese person (Damms-Machado *et al.* 2012); although, to note, nutritional deficiencies were present before the study and this may have influenced the findings. There is clearly a need for more research in this area to understand the requirements for vitamins and minerals in people with obesity, particularly during the weight loss phase and in those with higher BMIs.

Adverse events and attrition

Adverse event frequency is more extensively documented than 4 years ago (Leeds 2014). The largest dataset from the *Prevention of diabetes through lifestyle intervention and population studies in Europe and around the world* (*PREVIEW*) study (Christensen *et al.* 2018) (weight loss with TDR in 2224 participants with pre-diabetes) showed that the most common complaints were constipation (15%), fatigue/muscle weakness (9%), headache (8%) and dizziness (4%); in the *DROPLET* trial, the same side effects were reported (in 138 participants) but at half that frequency (8%, 5%, 3% and 2%, respectively) (Astbury *et al.* 2018). Constipation has long been recognised as a consequence of the large reduction in residual substrate entering the colon for fermentation and stool-bulking when using TDR. This can be overcome by providing additional stool-bulking dietary fibre (*e.g.* Psyllium husk) from the commencement of the diet, especially in those with a previous history of constipation, diverticular disease, diverticulitis or anal pathology. The fatigue or muscle weakness is a physiological response consistent with changes in muscle strength reported by Henriksen and colleagues, a subset of participants in the weight loss with TDR in people with knee OA trial (*CarOT*). Absolute muscle strength decreased by 3–4% although 'body mass normalised' muscle strength increased by 11–12% (Henriksen *et al.* 2012). Potential users of TDR need to be warned of the likelihood of these effects, particularly dizziness which may be more troublesome in the elderly and those treated with anti-hypertensive medications. Blood pressure is reduced rapidly in some individuals, and there is a risk of postural hypotension. Those with hypertension should be warned about dizziness on standing up, monitored more frequently than weekly initially and have their medications reviewed by their GP promptly. TDR caused gout at a rate of less than one in 1500 in women and one in 120 in men in the *PREVIEW* study (Christensen *et al.* 2018). There were no identified cases of gallstones in 2224 participants in the *PREVIEW* study but a large study from Sweden that showed the rate for hospitalisation for investigation and treatment of gallstones was three times higher after a VLED than after a 1200 kcal/day LED, although most cases occurred in the food re-introduction phase (Johansson *et al.* 2014b). Thus, it is wise to advise that there is a small risk of a gallstone event after a VLED and possibly after a LED.

A relatively high proportion of participants are retained in TDR trials. In the *LIGHT* long-term weight maintenance knee OA trial (Christensen *et al.* 2017b), 109 out of 153 entrants (71.2%) stayed in the programme for 3 years perhaps motivated by their preceding 10% weight loss that improved their mobility and reduced pain. The provision of TDR products and frequent contact with a healthcare professional certainly also played a part in this low attrition rate. In contrast, in the *PREVIEW* study of 1854 participants with pre-diabetes who started the 3-year conventional diet programme, 962 (52%) stayed in the programme for 3 years with less frequent contact and only conventional diet and lifestyle variables (Tucker 2018). Symptomatic improvement, especially in a chronic degenerative condition, may be a strong motivator for long-term compliance.

Patient views and experiences of formula diets

Currently, the assessment of patients' views and experiences of formula diets is limited within the scientific

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literature. A recent systematic review of the qualitative research on the experiences of people using VLEDs for weight loss identified only three qualitative studies (Ostberg *et al.* 2011; Love *et al.* 2016; Rehackova *et al.* 2017) that explored in-depth, subjects' experiences following a VLED (Harper *et al.* 2018). They reported that the VLED was easier to adhere to than initially thought. The rapid weight loss, feeling less hungry and the ease of use of the diet facilitated subjects' adherence. Furthermore, it gave them new insights into their relationship with food, which supports anecdotal reports from clinical practice. Other key factors identified that aided adherence included avoidance of tempting situations and environments (*e.g.* avoiding socials events and triggers for food consumption), planning ahead and self-distraction techniques. Therefore, educating subjects about behavioural techniques that could help them manage potential triggers for food consumption prior to starting a formula diet may aid weight loss and long-term maintenance. One key element reported by the subjects was the inclusion of group support sessions. Subjects reported that these provided a sense of community and also competition with each other, which was not possible with the one-to-one appointments. This is an important consideration when thinking about using formula diets in clinical practice.

In addition to the studies included in the systematic review by Harper *et al.* (2018), a recent study explored the psychosocial determinants of maintaining weight loss following a formula diet in subjects who were classified as either 'weight reducers' (>3% weight loss) or 'weight regainers' (>3% weight gain) at 52 weeks (Christensen *et al.* 2017a). The 'weight reducers' reported having a structured meal pattern, no comfort eating and less psychological stress compared with the 'weight regainers' (Christensen *et al.* 2017a). In addition, three key ingrained habits were identified which were calorie counting, choosing foods based on their nutrient content and using self-monitoring tools, which the authors termed the 'instrumentalisation of eating behaviour' (Christensen *et al.* 2017a). These three habits were similar to those factors identified in the National Control Weight Registry, which included eating a low-energy diet and self-monitoring weight (Wing & Phelan 2005), suggesting that these may be key to weight loss maintenance.

Gaps in knowledge

Despite increasing evidence for the efficacy of LEDs and VLEDs to achieve clinically significant weight loss, there are several areas where more work needs to be undertaken. There remains significant heterogeneity in the literature with regard to study methodology, particularly the time scale of the TDR phase, how best to reintroduce food following TDR, the most effective way to manage weight loss maintenance and in which circumstances a VLED or LED is used. As such, it currently remains challenging to develop best practice guidelines.

Rescue packages, which involve temporary use of the TDR phase or intermittent use of the formula product, have been shown to aid weight maintenance (Christensen *et al.* 2017b; Lean *et al.* 2017). However, when and how best to use rescue packages still requires further research.

Two areas of particular interest for the use of formula diets are chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NAFLD), both of which are highly prevalent within the obese and T2D patient population and can benefit significantly from weight loss. At present, however, there is limited evidence to support the use of formula diets within clinical practice for these conditions (Mulholland *et al.* 2012; Rolland *et al.* 2013; Brown & Taheri 2018).

Although defined within legislation, some aspects of the recommended nutritional composition of formula diets are based on weak experimental evidence. There is a clear need for further clinical studies to determine optimal diet composition during rapid weight loss in the TDR phase, with special reference to protein and lean mass reduction, essential fatty acid requirements and micronutrients, with studies on those with a BMI greater than 50 kg/m^2 particularly needed. More research is also needed on the optimal macronutrient composition to aid weight maintenance, medication prescribing practices both on commencing weight loss and on reintroducing conventional food, and optimal levels of physical activity during both weight loss and weight loss maintenance.

Although the *DiRECT* study was highly effective in achieving clinically significant outcomes, several questions remain unanswered. It remains unclear whether the use of the Counterweight-Plus Programme is a prerequisite to achieving the same clinical outcomes or whether this could be achieved within current clinical practice with a different structured programme. As each subject received around 20 contacts in the initial 12 months of the *DIRECT* trial, this is likely not to be achievable in the majority of clinical services. Furthermore, the *DiRECT* study was limited to those with T2D for less than 6 years, meaning that this dietary method cannot, at present, be recommended to people with more advanced T2D or those treated with insulin. However, research within this patient population is now complete and due for publication in the near future. With over three million people living with T2D in the UK, gaining a greater understanding of the characteristics of those individuals that achieve T2D remission on a formula diet will aid a more focussed approach; the pathophysiologic studies from *DiRECT* have highlighted some key factors, the challenge now is how best to translate these findings to clinical practice. In addition, there is need for the *DiRECT* study to be replicated in a more ethnically diverse population, as nearly all patients were white British (98.5%), meaning results at present are not generalisable to the wider British population with T2D. It is understood a study with these objectives is currently underway. Finally, as yet, the long-term effects of a LED TDR programme on T2D remission and on diabetes complications are not known (Diabetes UK 2018). Further studies will no doubt address some of these questions but presently it is important that healthcare professionals proceed with some caution when implementing formula diets in clinical practice.

Summary

The use of formula VLEDs and LEDs has been shown to effectively produce clinically significant weight loss of between 10% and 15% bodyweight for up to 12 months, and when combined with weight loss maintenance strategies can aid long-term weight maintenance for up to 4 years. Evidence has also grown for their effective use in obesity-related co-morbidities, particularly OSA and OA. Recent data showing that T2D can be put into remission using a formula LED in up to 46% of people may well change the landscape of T2D treatment in the coming few years.

Despite data demonstrating the effectiveness, safety and patient adherence and acceptability of VLEDs and LEDs, these dietary strategies are still being underutilised by healthcare professionals in clinical practice. The exact reasons for this are not well established, though may relate to healthcare professionals feeling that they lack the training and resources to put formula diets into practice and that it is outside their scope of practice. In addition, historical opinions of formula VLEDs and LEDs that they taste unpleasant are impossible to adhere to, result in weight regain, cost too much and have unacceptable side effects may also influence their use. The evidence base does not support these opinions and barriers clearly need to be broken down by educating healthcare professionals about the science in this area.

It is important to note that VLEDs and LEDs should be used as part of a multicomponent and multidisciplinary approach including physical activity, behaviour change and medical supervision (NICE 2014b). Prior to commencing a formula diet, a medical, dietetic and psychological assessment should ideally be done. It is evident that there is individual variability in success with formula diets and there is also variation in the metabolic response to weight loss with VLEDs and LEDs. Therefore, the setting of realistic expectations is key to avoiding disappointment and undue feeling of failure in the patient. Although some factors associated with a positive response to formula diets have been identified, more research is needed to fully establish how this dietary method could be best utilised within clinical practice.

Despite the gaps in knowledge, the current scientific evidence indicates that the use of formula VLEDs and LEDs with appropriate medical and dietetic support should now be considered a treatment option for T2D remission in those with recently diagnosed T2D, in those with obesity and in those with selected obesity-related co-morbidities.

Conflicts of interest

AB has received funding for investigator-initiated research through an educational grant and travel grants from Cambridge Weight Plan Ltd. ARL is salaried Medical Director of Cambridge Weight Plan that is an employee-owned trust, but holds no shares personally. ARL is also chairman of European industry group Total Diet Meal Replacement Europe.

References

Aaboe J, Bliddal H, Messier SP *et al.* (2011) Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis. *Osteoarthritis Cartilage* **19**: 822–8.

Afshin A, Forouzanfar MH, Reitsma MB *et al.* (2017) Health effects of overweight and obesity in 195 countries over 25 years. *The New England Journal of Medicine* **377**: 13–27.

Albu JB, Heilbronn LK, Kelley DE *et al.* (2010) Metabolic changes following a 1-year diet and exercise intervention in patients with type 2 diabetes. *Diabetes* **59**: 627–33.

Aller EE, Larsen TM, Claus H *et al.* (2014) Weight loss maintenance in overweight subjects on ad libitum diets with high or low protein content and glycemic index: the DIOGENES trial 12-month results. *International Journal of Obesity (London)* **38**: 1511–7.

Astbury NM, Aveyard P, Nickless A *et al.* (2018) Doctor referral of overweight people to low energy total diet replacement treatment

(DROPLET): pragmatic randomised controlled trial. *British Medical Journal* **362**: k3760.
Astrup A & Rossner S (2000) Lessons from obesity management programmes: greater initial weight loss improves long-term maintenance. *Obesity Reviews* **1**: 17–9.
Atukorala I, Makovey J, Lawler L *et al.* (2016) Is there a dose-response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? *Arthritis Care & Research* **68**: 1106–14.
Ballegaard C, Riss RGC, Bliddal H *et al.* (2014) Knee pain and inflammation in the infrapatellar fat pad estimated by conventional and dynamic contrast-enhanced magnetic resonance imaging in obese patients with osteoarthritis: a cross-sectional study. *Osteoarthritis Cartilage* **22**: 933–40.
Batterham RL & Cummings DE (2016) Mechanisms of diabetes improvement following bariatric/metabolic surgery. *Diabetes Care* **39**: 893–901.
Bischoff SC, Damms-Machado A, Betz C *et al.* (2012) Multicenter evaluation of an interdisciplinary 52-week weight loss program for obesity with regard to body weight, comorbidities and quality of life–a prospective study. *International Journal of Obesity (London)* **36**: 614–24.
Bliddal H, Leeds AR, Stigsgaard L *et al.* (2011) Weight loss as treatment for knee osteoarthritis symptoms in obese patients: 1-year results from a randomised controlled trial. *Annals of the Rheumatic Diseases* **70**: 1798–803.
Borg P, Kukkonen-Harjula K, Fogelholm M *et al.* (2002) Effects of walking or resistance training on weight loss maintenance in obese, middle-aged men: a randomized trial. *International Journal of Obesity and Related Metabolic Disorders* **26**: 676–83.
Brown A & Taheri S (2018) Very-low-energy diets for weight loss in patients with kidney disease. *Journal of Kidney Care* **3**: 14–22.
Brown A, Frost G & Taheri S (2015) Is there a place for low-energy formula diets in weight management. *British Journal of Obesity* **3**: 84–119.
Brown A, Guess N, Dornhorst A *et al.* (2017a) Insulin-associated weight gain in obese type 2 diabetes mellitus patients: what can be done? *Diabetes, Obesity & Metabolism* **19**: 1655–68.
Brown TJ, O'Malley C, Blackshaw J *et al.* (2017b) Exploring the evidence base for Tier 3 weight management interventions for adults: a systematic review. *Clinical Obesity* **7**: 260–72.
Calton JB (2010) Prevalence of micronutrient deficiency in popular diet plans. *Journal of the International Society of Sports Nutrition* **7**: 24.
Chaston TB, Dixon JB & O'Brien PE (2007) Changes in fat-free mass during significant weight loss: a systematic review. *International Journal of Obesity (London)* **31**: 743–50.
Christensen P, Bliddal H, Riecke BF *et al.* (2011) Comparison of a low-energy diet and a very low-energy diet in sedentary obese individuals: a pragmatic randomized controlled trial. *Clinical Obesity* **1**: 31–40.
Christensen P, Frederiksen R, Bliddal H *et al.* (2013) Comparison of three weight maintenance programs on cardiovascular risk, bone and vitamins in sedentary older adults. *Obesity (Silver Spring)* **21**: 1982–90.
Christensen PBH, Bartels E, Leeds A *et al.* (2014) Long-term intervention with weight loss in patients with concomitant obesity and knee osteoarthritis: the LIGHT study – a randomised clinical trial. T5: S25.54. *Obesity Reviews* **15**: 152.
Christensen BJ, Iepsen EW, Lundgren J *et al.* (2017a) Instrumentalization of eating improves weight loss maintenance in obesity. *Obesity Facts* **10**: 633–47.
Christensen P, Henriksen M, Bartels EM *et al.* (2017b) Long-term weight-loss maintenance in obese patients with knee osteoarthritis: a randomized trial. *American Journal of Clinical Nutrition* **106**: 755–63.
Christensen P, Meinert Larsen T, Westerterp-Plantenga M *et al.* (2018) Men and women respond differently to rapid weight loss: metabolic outcomes of a multi-centre intervention study after a low-energy diet in 2500 overweight, individuals with pre-diabetes (PREVIEW). *Diabetes, Obesity & Metabolism* **20**: 2840–51.
Christiansen MP, Linfoot PA, Neese RA *et al.* (2000) Effect of dietary energy restriction on glucose production and substrate utilization in type 2 diabetes. *Diabetes* **49**: 1691–9.
CODEX CAC (1995) Codex standard for formula foods for use in very low energy diets for weight reduction – CODEX STAN 203-1995. Rome, Italy.
Colquitt JL, Pickett K, Loveman E *et al.* (2014) Surgery for weight loss in adults. *Cochrane Database of Systematic Reviews* CD003641.
Coutinho SR, With E, Rehfeld JF *et al.* (2017) The impact of rate of weight loss on body composition and compensatory mechanisms during weight reduction: A randomized control trial. *Clinical Nutrition* **37**: 1154–62.
Cross M, Smith E, Hoy D *et al.* (2014) The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Annals of the Rheumatic Diseases* **73**: 1323–30.
Damms-Machado A, Weser G & Bischoff SC (2012) Micronutrient deficiency in obese subjects undergoing low calorie diet. *Nutrition Journal* **11**: 34.
Diabetes UK (2018) Diabetes UK interim position statement on remission in adults with Type 2 diabetes. pp. 1–6.
Dixon JB, O'Brien PE, Playfair J *et al.* (2008) Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *Journal of the American Medical Association* **299**: 316–23.
Doble B, Wordsworth S, Rogers CA *et al.* (2017) What are the real procedural costs of bariatric surgery? A systematic literature review of published cost analyses. *Obesity Surgery* **27**: 2179–92.
Dyson PA, Twenefour D, Breen C *et al.* (2018) Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. *Diabetic Medicine* **35**: 541–7.
EFSA NDA Panel (European Food Safety Authority Panel on Dietetic Products Nutrition and Allergies) (2015) Scientific Opinion on the essential composition of total diet replacements for weight control. *EFSA Journal* **13**: 3957.
Esposito K, Maiorino MI, Petrizzo M *et al.* (2014) The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: follow-up of a randomized trial. *Diabetes Care* **37**: 1824–30.
Fogelholm M, Kukkonen-Harjula K, Nenonen A *et al.* (2000) Effects of walking training on weight maintenance after a very-low-energy diet in premenopausal obese women: a randomized controlled trial. *Archives of Internal Medicine* **160**: 2177–84.
Franz MJ, Boucher JL, Rutten-Ramos S *et al.* (2015) Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of

randomized clinical trials. *Journal of the Academy of Nutrition and Dietetics* **115**: 1447–63.
Gardner CD, Kim S, Bersamin A *et al.* (2010) Micronutrient quality of weight-loss diets that focus on macronutrients: results from the A TO Z study. *American Journal of Clinical Nutrition* **92**: 304–12.
Garvey WT, Mechanick JI, Brett EM *et al.* (2016) American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrine Practice* **22**(Suppl. 3): 1–203.
Geyer PE, Wewer Albrechtsen NJ, Tyanova S *et al.* (2016) Proteomics reveals the effects of sustained weight loss on the human plasma proteome. *Molecular Systems Biology* **12**: 901.
Gibson AA, Seimon RV, Lee CMY *et al.* (2014) Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obesity Reviews* **16**: 64–76.
Gregg EW, Chen H, Wagenknecht LE *et al.* (2012) Association of an intensive lifestyle intervention with remission of type 2 diabetes. *Journal of the American Medical Association* **308**: 2489–96.
Gripeteg L, Torgerson J, Karlsson J *et al.* (2010) Prolonged refeeding improves weight maintenance after weight loss with very-low-energy diets. *British Journal of Nutrition* **103**: 141–8.
Hall KD, Sacks G, Chandramohan D *et al.* (2011) Obesity 3 quantification of the effect of energy imbalance on bodyweight. *Lancet* **378**: 826–37.
Hallberg SJ, McKenzie AL, Williams PT *et al.* (2018) Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. *Diabetes Therapy* **9**: 583–612.
Hammer S, Snel M, Lamb HJ *et al.* (2008) Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. *Journal of the American College of Cardiology* **52**: 1006–12.
Harper C, Maher J, Grunseit A *et al.* (2018) Experiences of using very low energy diets for weight loss by people with overweight or obesity: a review of qualitative research. *Obesity Reviews* **19**: 1412–23.
Haslam DW, Waine C, Leeds AR (2010) *Medical Management During Effective Weight-Loss*. National Obesity Forum: London.
Henriksen M, Christensen R, Danneskiold-Samsoe B *et al.* (2012) Changes in lower extremity muscle mass and muscle strength after weight loss in obese patients with knee osteoarthritis: a prospective cohort study. *Arthritis and Rheumatism* **64**: 438–42.
Henry RR, Wiest-Kent TA, Scheaffer L *et al.* (1986) Metabolic consequences of very-low-calorie diet therapy in obese non-insulin-dependent diabetic and nondiabetic subjects. *Diabetes* **35**: 155–64.
Iepsen EW, Lundgren J, Dirksen C *et al.* (2015) Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss. *International Journal of Obesity (London)* **39**: 834–41.
Iepsen EW, Lundgren J, Holst JJ *et al.* (2016) Successful weight loss maintenance includes long-term increased meal responses of GLP-1 and PYY3-36. *European Journal of Endocrinology* **174**: 775–84.
Jackness C, Karmally W, Febres G *et al.* (2013) Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and beta-cell Function in type 2 diabetic patients. *Diabetes* **62**: 3027–32.
Jazet IM, Ouwens DM, Schaart G *et al.* (2005) Effect of a 2-day very low-energy diet on skeletal muscle insulin sensitivity in obese type 2 diabetic patients on insulin therapy. *Metabolism* **54**: 1669–78.
Jazet IM, de Craen AJ, van Schie EM *et al.* (2007) Sustained beneficial metabolic effects 18 months after a 30-day very low calorie diet in severely obese, insulin-treated patients with type 2 diabetes. *Diabetes Research and Clinical Practice* **77**: 70–6.
Jazet IM, Schaart G, Gastaldelli A *et al.* (2008) Loss of 50% of excess weight using a very low energy diet improves insulin-stimulated glucose disposal and skeletal muscle insulin signalling in obese insulin-treated type 2 diabetic patients. *Diabetologia* **51**: 309–19.
Jensen P & Skov L (2016) Psoriasis and obesity. *Dermatology* **232**: 633–9.
Jensen P, Zachariae C, Christensen R *et al.* (2013) Effect of weight loss on the severity of psoriasis: a randomized clinical study. *Journal of the American Medical Association: Dermatology* **149**: 795–801.
Jensen P, Zachariae C, Christensen R *et al.* (2014) Effect of weight loss on the cardiovascular risk profile of obese patients with psoriasis. *Acta Dermato Venereologica* **94**: 691–4.
Jensen P, Christensen R, Zachariae C *et al.* (2016) Long-term effects of weight reduction on the severity of psoriasis in a cohort derived from a randomized trial: a prospective observational follow-up study. *American Journal of Clinical Nutrition* **104**: 259–65.
Johansson K, Neovius M, Lagerros YT *et al.* (2009) Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial. *British Medical Journal* **339**: 1–9.
Johansson K, Hemmingsson E, Harlid R *et al.* (2011) Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study. *British Medical Journal* **342**: 1–9.
Johansson K, Neovius M & Hemmingsson E (2014a) Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. *American Journal of Clinical Nutrition* **99**: 14–23.
Johansson K, Sundstrom J, Marcus C *et al.* (2014b) Risk of symptomatic gallstones and cholecystectomy after a very-low-calorie diet or low-calorie diet in a commercial weight loss program: 1-year matched cohort study. *International Journal of Obesity (London)* **38**: 279–84.
Johnston BC, Kanters S, Bandayrel K *et al.* (2014) Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *Journal of the American Medical Association* **312**: 923–33.
Kajaste S, Brander PE, Telakivi T *et al.* (2004) A cognitive-behavioral weight reduction program in the treatment of obstructive sleep apnea syndrome with or without initial nasal CPAP: a randomized study. *Sleep Medicine* **5**: 125–31.
Kent SMB, Astbury N, Aveyard P *et al.* (2018) Is a total diet replacement programme cost effective to treat obesity? Abstracts from the 5th UK Congress on Obesity 2018: Oral Presentation Abstracts. *International Journal of Obesity Supplements* **8**: 6–13.
Larsen RN, Mann NJ, Maclean E *et al.* (2011) The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. *Diabetologia* **54**: 731–40.
Lean M (2011) VLED and formula LED in the management of type 2 diabetes: defining the clinical need and research requirements. *Clinical Obesity* **1**: 41–9.
Lean M, Brosnahan N, McLoone P *et al.* (2013) Feasibility and indicative results from a 12-month low-energy liquid diet

treatment and maintenance programme for severe obesity. *British Journal of General Practice* **63**: e115–24.

Lean ME, Leslie WS, Barnes AC *et al.* (2017) Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* **391**: 541–51.

Lee Y, Hirose H, Ohneda M *et al.* (1994) Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships. *Proceedings of the National Academy of Sciences of the United States of America* **91**: 10878–82.

Lee Y, Lingvay I, Szczepaniak LS *et al.* (2010) Pancreatic steatosis: harbinger of type 2 diabetes in obese rodents. *International Journal of Obesity (London)* **34**: 396–400.

Leeds AR (2014) Formula food-reducing diets: a new evidence-based addition to the weight management tool box. *Nutrition Bulletin* **39**: 238–46.

Leslie WS, Ford I, Sattar N *et al.* (2016) The Diabetes Remission Clinical Trial (DiRECT): protocol for a cluster randomised trial. *BMC Family Practice* **17**: 20.

Lim EL, Hollingsworth KG, Aribisala BS *et al.* (2011) Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* **54**: 2506–14.

Lingvay I, Esser V, Legendre JL *et al.* (2009) Noninvasive quantification of pancreatic fat in humans. *Journal of Clinical Endocrinology and Metabolism* **94**: 4070–6.

Lips MA, de Groot GH, van Klinken JB *et al.* (2014) Calorie restriction is a major determinant of the short-term metabolic effects of gastric bypass surgery in obese type 2 diabetic patients. *Clinical Endocrinology - Oxford* **80**: 834–42.

Love JG, McKenzie JS, Nikokavoura EA *et al.* (2016) The experiences of women with polycystic ovary syndrome on a very low-calorie diet. *International Journal of Women's Health* **8**: 299–310.

MacLean PS, Wing RR, Davidson T *et al.* (2015) NIH Working Group Report: innovative research to improve maintenance of weight loss. *Obesity* **23**: 7–15.

McCombie L, Brosnahan N, Ross H *et al.* (2018) Filling the intervention gap: service evaluation of an intensive nonsurgical weight management programme for severe and complex obesity. *Journal of Human Nutrition and Dietetics*. https://doi.org/10.1111/jhn.12611

Miras AD & le Roux CW (2013) Mechanisms underlying weight loss after bariatric surgery. *Nature Reviews Gastroenterology & Hepatology* **10**: 575–84.

Mulholland Y, Nicokavoura E, Broom J *et al.* (2012) Very-low-energy diets and morbidity: a systematic review of longer-term evidence. *British Journal of Nutrition* **108**: 832–51.

Nerfeldt P, Nilsson BY, Mayor L *et al.* (2010) A two-year weight reduction program in obese sleep apnea patients. *Journal of Clinical Sleep Medicine* **6**: 479–86.

NICE (National Institute for Health and Care Excellence) (2014a) *Osteoarthritis: Care and Management in Adults. Clinical Guideline*. National Institute for Health and Care Excellence (UK), National Clinical Guideline Centre: London.

NICE (National Institute for Health and Care Excellence) (2014b) *Obesity: Identification, Assessment and Management of Overweight and Obesity in Children, Young People and Adults: Partial Update of CG43*. National Institute for Health and Care Excellence (UK): London.

Nield L, Moore HJ, Hooper L *et al.* (2007) Dietary advice for treatment of type 2 diabetes mellitus in adults. *Cochrane Database of Systematic Reviews* (**3**): CD004097.

Nielsen LV, Nielsen MS, Schmidt JB *et al.* (2016) Efficacy of a liquid low-energy formula diet in achieving preoperative target weight loss before bariatric surgery. *Journal of Nutritional Science* **5**: e22.

NIH (National Institutes of Health) (1993) Very low-calorie diets. National Task Force on the Prevention and Treatment of Obesity, National Institutes of Health. *Journal of the American Medical Association* **270**: 967–74.

Nyberg ST, Batty GD, Pentti J *et al.* (2018) Obesity and loss of disease-free years owing to major non-communicable diseases: a multicohort study. *Lancet Public Health* **3**: e490–7.

Olsen RH, Pedersen LR, Jurs A *et al.* (2015) A randomised trial comparing the effect of exercise training and weight loss on microvascular function in coronary artery disease. *International Journal of Cardiology* **185**: 229–35.

Ostberg AL, Wikstrand I & Bengtsson Bostrom K (2011) Group treatment of obesity in primary care practice: a qualitative study of patients' perspectives. *Scandinavian Journal of Public Health* **39**: 98–105.

Parretti HM, Jebb SA, Johns DJ *et al.* (2016) Clinical effectiveness of very-low-energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials. *Obesity Reviews* **17**: 225–34.

Pedersen LR, Olsen RH, Jurs A *et al.* (2015) A randomised trial comparing weight loss with aerobic exercise in overweight individuals with coronary artery disease: the CUT-IT trial. *European Journal of Preventive Cardiology* **22**: 1009–17.

Pedersen LR, Olsen RH, Anholm C *et al.* (2016) Weight loss is superior to exercise in improving the atherogenic lipid profile in a sedentary, overweight population with stable coronary artery disease: a randomized trial. *Atherosclerosis* **246**: 221–8.

Primary Care Sciences Oxford (2018) Total Diet Replacement Programes ("Crash Diets") Resources for Health Professionals.

Purcell K, Sumithran P, Prendergast LA *et al.* (2014) The effect of rate of weight loss on long-term weight management: a randomised controlled trial. *Lancet Diabetes & Endocrinology* **2**: 954–62.

Rehackova L, Araujo-Soares V, Adamson AJ *et al.* (2017) Acceptability of a very-low-energy diet in Type 2 diabetes: patient experiences and behaviour regulation. *Diabetic Medicine* **34**: 1554–67.

Riis RG, Gudbergsen H, Henriksen M *et al.* (2016) Synovitis assessed on static and dynamic contrast-enhanced magnetic resonance imaging and its association with pain in knee osteoarthritis: a cross-sectional study. *European Journal of Radiology* **85**: 1099–108.

Rolland C, Mavroeidi A, Johnston KL *et al.* (2013) The effect of very low-calorie diets on renal and hepatic outcomes: a systematic review. *Diabetes, Metabolic Syndrome and Obesity* **6**: 393–401.

Rolland C, Johnston KL, Lula S *et al.* (2014) Long-term weight loss maintenance and management following a VLCD: a 3-year outcome. *International Journal of Clinical Practice* **68**: 379–87.

Rubino F, Nathan DM, Eckel RH *et al.* (2017) Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. *Obesity Surgery* **27**: 2–21.

Rushing J, Wing R, Wadden TA *et al.* (2017) Cost of intervention delivery in a lifestyle weight loss trial in type 2 diabetes: results from the Look AHEAD clinical trial. *Obesity Science & Practice* **3**: 15–24.

Saris WH (2001) Very-low-calorie diets and sustained weight loss. *Obesity Research* **9**(Suppl. 4): 295s–301s.

Schauer PR, Bhatt DL, Kirwan JP *et al.* (2017) Bariatric surgery versus intensive medical therapy for diabetes – 5-year outcomes. *New England Journal of Medicine* **376**: 641–51.

SIGN (Scottish Intercollegiate Guidelines Network) (2010) *Scottish Intercollegiate Guidelines Network 115 Management of Obesity: A National Clinical Guideline* (Scotland, N. ed.). SIGN: Edinburgh

Snel M, van Diepen JA, Stijnen T *et al.* (2011) Immediate and long-term effects of addition of exercise to a 16-week very low calorie diet on low-grade inflammation in obese, insulin-dependent type 2 diabetic patients. *Food and Chemical Toxicology* **49**: 3104–11.

Snel M, Gastaldelli A, Ouwens DM *et al.* (2012a) Effects of adding exercise to a 16-week very low-calorie diet in obese, insulin-dependent type 2 diabetes mellitus patients. *Journal of Clinical Endocrinology and Metabolism* **97**: 2512–20.

Snel M, Jonker JT, Hammer S *et al.* (2012b) Long-term beneficial effect of a 16-week very low calorie diet on pericardial fat in obese type 2 diabetes mellitus patients. *Obesity (Silver Spring)* **20**: 1572–6.

Snel M, Sleddering MA, Vd Peijl ID *et al.* (2012c) Quality of life in type 2 diabetes mellitus after a very low calorie diet and exercise. *European Journal of Internal Medicine* **23**: 143–9.

Steven S & Taylor R (2015) Restoring normoglycaemia by use of a very low calorie diet in long- and short-duration Type 2 diabetes. *Diabetic Medicine* **32**: 1149–55.

Steven S, Hollingsworth KG, Al-Mrabeh A *et al.* (2016a) Very-low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiologic changes in responders and nonresponders. *Diabetes Care* **39**: 808–15.

Steven S, Hollingsworth KG, Small PK *et al.* (2016b) Calorie restriction and not glucagon-like peptide-1 explains the acute improvement in glucose control after gastric bypass in Type 2 diabetes. *Diabetic Medicine* **33**: 1723–31.

Sumithran P, Prendergast LA, Delbridge E *et al.* (2011) Long-term persistence of hormonal adaptations to weight loss. *New England Journal of Medicine* **365**: 1597–604.

Sumithran P, Prendergast LA, Delbridge E *et al.* (2013) Ketosis and appetite-mediating nutrients and hormones after weight loss. *European Journal of Clinical Nutrition* **67**: 759–64.

Taylor R (2008) Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. *Diabetologia* **51**: 1781–9.

Taylor R, Al-Mrabeh A, Zhyzhneuskaya S *et al.* (2018) Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for beta cell recovery. *Cell Metabolism* **28**: 547–56.

Terranova CO, Brakenridge CL, Lawler SP *et al.* (2015) Effectiveness of lifestyle-based weight loss interventions for adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetes, Obesity and Metabolism* **17**: 371–8.

Tsai AG & Wadden TA (2006) The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity (Silver Spring)* **14**: 1283–93.

Tucker M (2018) Fast Initial Weight Loss May Be Key to Diabetes Prevention. WebMD, LLC, Medscape Medical News.

Tuomilehto HP, Seppa JM, Partinen MM *et al.* (2009) Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine* **179**: 320–7.

Tushuizen ME, Bunck MC, Pouwels PJ *et al.* (2007) Pancreatic fat content and beta-cell function in men with and without type 2 diabetes. *Diabetes Care* **30**: 2916–21.

Unger RH (1995) Lipotoxicity in the pathogenesis of obesity-dependent NIDDM. Genetic and clinical implications. *Diabetes* **44**: 863–70.

Vink RG, Roumans NJT, Arkenbosch LAJ *et al.* (2016) The effect of rate of weight loss on long-term weight regain in adults with overweight and obesity. *Obesity* **24**: 321–7.

Wadden TA & Stunkard AJ (1986) Controlled trial of very low calorie diet, behavior therapy, and their combination in the treatment of obesity. *Journal of Consulting and Clinical Psychology* **54**: 482–8.

Wadden TA, Neiberg RH, Wing RR *et al.* (2011) Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring)* **19**: 1987–98.

Webster JD, Hesp R & Garrow JS (1984) The composition of excess weight in obese women estimated by body density, total body water and total body potassium. *Human Nutrition. Clinical Nutrition* **38**: 299–306.

Welbourn R, Le Roux CW, Owen-Smith A *et al.* (2016) Why the NHS should do more bariatric surgery; how much should we do? *British Medical Journal* **353**: i1472.

Wing RR & Phelan S (2005) Long-term weight loss maintenance. *The American Journal of Clinical Nutrition* **82**: 222s–225s.

Wing RR, Marcus MD, Salata R *et al.* (1991) Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. *Archives of Internal Medicine* **151**: 1334–40.

Wing RR, Blair E, Marcus M *et al.* (1994) Year-long weight loss treatment for obese patients with type II diabetes: does including an intermittent very-low-calorie diet improve outcome? *American Journal of Medicine* **97**: 354–62.

World Health Organization (2018a) *Noncommunicable Diseases*. World Health Organization: Geneva.

World Health Organization (2018b) *Overweight and Obesity World Health Organization*. World Health Organization: Geneva.

Xin Y, Davies A, McCombie L *et al.* (2018) Within-trial cost and 1-year cost-effectiveness of the DiRECT/Counterweight-Plus weight-management programme to achieve remission of type 2 diabetes. *The Lancet Diabetes & Endocrinology*. https://doi.org/10.1016/S2213-8587(18)30346-2.

Yu J, Zhou X, Li L *et al.* (2015) The long-term effects of bariatric surgery for type 2 diabetes: systematic review and meta-analysis of randomized and non-randomized evidence. *Obesity Surgery* **25**: 143–58.