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

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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

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...
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/m²), 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 body-weight 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)

<table>
<thead>
<tr>
<th>Weight loss strategies</th>
<th>Follow-up (months)</th>
<th>Weight loss (kg)</th>
<th>Fasting blood glucose (mmol/l)</th>
<th>Blood pressure (mmHg)</th>
<th>Lipids (mmol/l)</th>
<th>Waist circumference (cm)</th>
<th>Attrition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLED + TDR*</td>
<td>1 to 4</td>
<td>12.4 to 27.2</td>
<td>−1.1 to −1.5</td>
<td>−11.1 to −21</td>
<td>−0.73 to −1.3</td>
<td>−8.6 to −25</td>
<td>4 to 10</td>
</tr>
<tr>
<td>VLED + Maintenance phase</td>
<td>2 to 33</td>
<td>4.1 to 15.4</td>
<td>−0.2 to −3.8</td>
<td>−16 to 1</td>
<td>−0.02 to −1.1</td>
<td>−7 to −12</td>
<td>4 to 10</td>
</tr>
<tr>
<td>LED + TDR†</td>
<td>4 to 48</td>
<td>7.9 to 12.4</td>
<td>−0.17 to −1.3</td>
<td>−26 to 17</td>
<td>−0.84 to −0.1</td>
<td>−8.1 to −13</td>
<td>7 to 17</td>
</tr>
<tr>
<td>LED + Maintenance phase</td>
<td></td>
<td>9.9 to 12.4</td>
<td>−0.18 to −2.4</td>
<td>−13 to −7.8</td>
<td>−1.02 to 0.04</td>
<td>−8.9 to −11.3</td>
<td>0 to 52</td>
</tr>
</tbody>
</table>

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 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. (2017ab, 2018), McCombie et al. (2018), and Astbury et al. (2018).

Weight loss and type 2 diabetes remission

The idea that T2D can be put into remission using diet-alone methods is not new. In an ancillary analysis of the Look AHEAD cohort, subjects in the intensive standardised care (2%) and those who received multicomponent lifestyle intervention group were more likely to experience T2D remission (11.5%). Patients receiving a formula diet whilst undergoing intensive lifestyle intervention had the greatest improvement in HbA1c (1001–200 kcal/day), although fasting blood glucose (1001–300 kcal/day) produced greater weight loss, less than 100 kcal/day and HbA1c levels did not differ between the groups at 1 year. Those who lost the most weight had the greatest improvement in their HbA1c levels (Wing et al., 1994).
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, adaptations 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 islets 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 nor-
malisation of fasting plasma glucose (<7 mmol/l) fol-
lowing 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 glu-
cose 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 improve-
ments 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, impor-
tantly, 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 num-
bers, 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, fol-
lowed by a long-term programme of weight loss main-
tenance 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 pri-
mary 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 partici-
pants with T2D were recruited from 49 general prac-
tices and randomised to either best practice NHS care
alone (control group) or best practice NHS care plus
an intensive structured weight management pro-
grame (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 pro-
grame. At 12 months, in an intention to treat analy-
sis, 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 per-
centage of people with T2D within a primary care set-
ting 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 differ-
ences 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 composi-
tion, surrogate markers of CVD including blood pres-
sure, 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 indi-
cates that the subjects had residual pancreatic func-
tion, something that not all advanced T2D patients
will have, therefore questioning the validity and
transferability of the findings. Despite these metho-
dological 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/m²) 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/m²) 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

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**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, while 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. 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 et al. 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
Formula diets – an update on the evidence

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/m² 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

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.
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.

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