Is there a place for low-energy formula diets in weight management?

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While reduction in energy intake is key to weight loss, it is challenging in practice to achieve a sufficient calorie deficit to achieve clinically significant weight loss. With indicators that a greater weight loss within the first year is a good predictor of long-term weight loss maintenance, the use of dietary methods to give a substantial early energy deficit could be beneficial. Low-energy (800–1200 kcal/day) formula diets (LEDs) and very-low-energy (<800 kcal/day) formula diets (VLEDs) have recently gained popularity in clinical practice as a tool to enable patients to achieve this substantial calorie deficit and, therefore, lose a significant amount of weight, with consequent improvements in obesity-related comorbidities. This review examines the current evidence for the use of LEDs and VLEDs for weight loss and improvements in obesity-related comorbidities, while helping to inform clinicians on their potential use in clinical practice.

Obesity has reached epidemic proportions worldwide, necessitating effective weight loss interventions and strategies for weight loss maintenance. Evidence shows that traditional popular dietary approaches produce, at best, between 5.3 and 7.27 kg of weight loss at 12 months (Avenell et al, 2004; Johnston et al, 2014), and an even lower degree of weight loss in primary care (Jolly et al, 2011). While a 5–10% weight loss has significant health benefits, it may be insufficient to give sustained and perceptible benefits for people with greater degrees of obesity (BMI ≥35 kg/m²) complicated by serious medical complications (SIGN, 2010). Currently, bariatric surgery appears to be the most effective therapy in terms of both sustained weight loss and treatment of comorbidities in severe obesity (Buchwald et al, 2004; Sjöström, 2013). When compared with non-surgical interventions, the weight loss achieved by bariatric surgery is associated with superior weight reduction, improved sleep quality, improved quality of life, and better glycaemic control (Dixon et al, 2008; Schauer et al, 2014). However, notwithstanding the methodological issues inherent in studies of bariatric surgery, not every patient wishes to undergo these procedures and, despite guidelines from NICE and other organisations, lack of funding limits accessibility to bariatric surgery, with only 1–2% of eligible patients receiving it (Dixon et al, 2011).

While the causes and pathophysiology of obesity are complex and still poorly understood (Cope and Allison, 2006), obesity primarily results from excessive calorie intake compared to calorie expenditure. With a heavier, ageing population with increased rates of osteoarthritis and limited mobility compared with the past (Leeds, 2014), effective dietary manipulation is crucial for obesity management in the vast majority of patients in clinical weight management services. Conventional dietary approaches lead to weight loss of only 0.5–1.0 kg per week, making them a daunting task for individuals who need to lose a lot of weight. Low-energy formula diets (LEDs), however, are able to create dietary energy deficits similar to those
achieved following bariatric surgery, and they have the potential to fill this therapeutic void between surgery and traditional therapy.

Very-low-energy and low-energy formula diets

Very-low-energy formula diets (VLEDs) are defined as hypo-calorific diets that provide 450–800 kcal (1884–3350 kJ) per day and replace the whole diet with prepared formula, usually in the form of liquid shakes, soups and bars (Atkinson et al, 1993; Codex Alimentarius, 1995; NICE, 2014). These are enriched by high-biological-value protein and provide 100% of the Dietary Reference Value for vitamins and minerals within a defined number of servings. Previously, a minimum daily energy intake of 450 kcal was suggested; this has recently been revised by the European Commission, which now recommends that a minimum of 600 kcal/day should be provided (European Food Safety Authority, 2015). In comparison, LEDs provide 800–1200 kcal (3350–5021 kJ) per day, with each meal replacement needing to provide 200–400 kcal per meal (Codex Alimentarius, 1991).

Within the medical literature, the terms “very-low-calorie” and “very-low-energy” have often been used interchangeably. As calories are units of energy, however, the latter is the preferred definition (Scientific Cooperation Committee, 2002) and will be used in this review. VLEDs have been reported in the medical literature for over 85 years. Evans and Strang (1929) published data on a ketogenic diet providing 6–8 kcal/kg, with 35% and 38% of the calories coming from protein and fat, respectively. They reported on more than 100 patients, who benefited from excellent weight loss with minimal side-effects. In the 1970s, VLEDs were popularised in the publication The Last Chance Diet (Linn, 1976). Original formulations not only included low-biological-value protein (hydrolysed collagen) but were also deficient in electrolytes and minerals, and they resulted in at least 60 fatalities owing to intractable ventricular arrhythmias (Sours et al, 1981; Wadden et al, 1983a). During this same period, formulations were developed that eliminated the previously seen arrhythmias (Felig, 1984). Since then, there has been a substantial amount of research within this area regarding optimal composition to minimise protein turnover, maintain nitrogen balance and ensure that essential micronutrient requirements are met.

Both LEDs and VLEDs are designed to produce rapid weight loss while maintaining fat-free body mass. VLEDs are designed to induce ketosis, during which controlled fasting and restriction of dietary carbohydrate causes fatty acid oxidation in the liver to form transformable energy, while also mediating suppression of ghrelin (Atkinson et al, 1993, Sumithran et al, 2013). However, owing to higher energy intakes, these effects might not be as prevalent in LEDs. LEDs are regulated in the EU by Directive 96/8/EC and by the European Food Safety Authority (EFSA). Compositional, labelling and advertising requirements for the use of LED total meal replacements are outlined within the Directive. Remarkably, VLEDs were not included within the original EU Directive, although they were subject to regulation and recommendations within the Codex Alimentarius Standard in the UK.

Recently, the European Commission requested that the EFSA provide a scientific opinion on the essential composition of total diet replacements for weight control and update the Directive to include VLEDs. The EFSA proposed several key recommendations (EFSA, 2015):

- Formulations should include the following:
  - Between 75 g and 105 g of high-quality protein per day, to maintain protein turnover.
  - A minimum of 30 g of digestible carbohydrate per day.
  - At least 11 g of linoleic acid and 1.4 g of alpha-linolenic acid per day.
  - A minimum of around 20 g of total fat per day, to ensure sufficient levels of essential fatty acids.
  - A minimum energy content of 600 kcal (2510 kJ) per day.
  - Daily micronutrient intake derived from Population Reference Intakes or Adequate Intakes, based on previous opinion.

- Individualised specialist medical advice is required for individuals with obesity-related comorbidities.
- Fluid intake during energy restriction should be 2.5 L/day for men and 2.0 L/day for women.

Owing to a lack of scientific evidence, no recommendations were made for minimum fibre intake; however, additional fibre is often provided,
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Page points
1. Both LEDs and VLEDs have been shown to produce significant weight loss over periods of 4–24 weeks, with data suggesting that greater weight loss occurs with longer diet durations.
2. Contrary to the expectation that greater energy restriction should lead to greater weight loss, there is little evidence that VLEDs produce greater weight loss than LEDs in the long term.
3. Recent evidence suggests that VLEDs can be effective in promoting long-term weight loss and maintenance, but only if supported with behaviour change techniques, especially around the time of reintroducing conventional food after the diet.

with around 7–10 g advised (Saris, 2001). Notably, legislation concerning the definition, composition, labelling, directions of use and availability of LEDs varies considerably across Europe and worldwide (Scientific Cooperation Committee, 2002).

Effects on weight loss
Short-term weight loss
Studies have shown that both VLEDs and LEDs are effective at promoting significant weight loss in the short term (up to 24 weeks), with concomitant improvements in obesity-related comorbidities (Atkinson, 1993; Johansson et al, 2009; Christensen et al, 2011; Mulholland et al, 2012). In the medical literature, the length of time on these diets varied between 4 and 24 weeks (Wadden et al, 1983b), with initial weight losses of 1.4–2.5 kg per week and suggestions that the longer the period of calorie restriction the greater the weight loss (Saris, 2001); however, prolonged calorie restriction can potentially affect compliance in the long term.

Despite the theoretical idea that VLEDs should produce greater weight loss because of greater energy restriction, this has not been shown to be the case over the long term (Saris, 2001; Norris et al, 2005; Lin et al, 2009; Christensen et al, 2011). In a meta-analysis of six randomised controlled trials, initial short-term weight loss was significantly greater following VLEDs compared to LEDs (16.1% vs. 9.7% of initial weight; Tsai and Wadden, 2006). This difference, however, was not sustained over time. A concern is that only one of the studies used an intention-to-treat (ITT) analysis, whereas the others biased the results by only analysing completers.

The lack of short-term difference was further demonstrated by a randomised controlled trial (Christensen et al, 2011). Here, at both 8 weeks and 16 weeks, there was no significant difference in weight loss between participants who used a VLED (420–554 kcal/day) and those who used an LED (810 kcal/day).

In clinical practice, if rapid weight loss is required (e.g. for a total knee replacement), using a formula diet for a period of 8–12 weeks has clear benefits (Leeds, 2014; NICE, 2014).

Long-term weight loss and maintenance
In the long term, weight loss with VLEDs and LEDs has been shown to be similar, owing to greater weight regain following cessation of a VLED. In Tsai and Wadden’s (2006) systematic review, over a mean follow-up of 1.9 years, the mean long-term weight loss was 6.3±3.2% and 5.0±4.0% in the VLED and LED groups, respectively, with the VLED group having regained 62% of the weight loss compared to 41% in the LED group.

Often the challenge with weight maintenance begins during the reintroduction of conventional food after the diet, especially if the individuals have not addressed the reasons for their initial weight gain. The use of behavioural techniques alongside formula diets are essential to aid weight loss maintenance and help the participants address their relationship with food, while also losing weight. Three recent studies, including two systematic reviews, have shown that long-term weight loss maintenance is possible following a VLED with the addition of weight loss maintenance strategies (Mulholland et al, 2012; Christensen et al, 2014; Johansson et al, 2014). Exercise, behaviour change therapy, medication and a longer reintroduction phase post-VLED all helped people to maintain greater weight loss (Mulholland et al, 2012). These observations are further supported by studies showing that anti-obesity drugs, extended use of low-energy meal replacements (one per day) and high-protein diets are associated with improved weight loss maintenance (Christensen et al, 2014; Johansson et al, 2014). Interestingly, in these studies, exercise did not result in significant improvements (Johansson et al, 2014). It must be noted that two of the three drug studies reviewed by Johansson and colleagues involved sibutramine, a drug that was withdrawn in 2010.

The commonly held belief that slow weight loss is better preserved than more rapid loss is in contrast to recent evidence, which shows a positive correlation between larger initial weight loss and long-term weight maintenance (Astrup and Rössner, 2000; Wadden et al, 2011; Rolland et al, 2014). The Look AHEAD study, which compared an intensive lifestyle intervention with conventional education and diabetes support in over 5000 people with type 2 diabetes, showed that the greatest determinant of weight maintenance at 4 years was the loss of ≥10% of baseline weight within the first year (Wadden et al, 2011). More
support for this position comes from a randomised trial of 204 participants comparing rates of weight regain following a weight loss of ≥12.5% using either a rapid (12-week) or gradual (36-week) weight loss programme (Purcell et al., 2014). The rate of weight loss did not affect the degree of weight regain over a 144-week period, with both groups regaining 76.3% of the weight loss in the ITT analysis. Therefore, interventions that enable a greater initial weight loss could be more effective in terms of long-term weight maintenance.

The place of low-energy formula diets in clinical practice
At present, the use of VLEDs and LEDs within clinical practice remains a rarity amongst healthcare professionals. The belief that the high rate of weight loss and the regain of weight following cessation are detrimental remains a concern (NICE, 2014); however, this position has started to be challenged (Christensen et al., 2014; Johansson et al., 2014; Rolland et al., 2014). Furthermore, the vast majority of research for formula diets has been in people with a BMI between 30 and 40 kg/m², while the evidence for their use within the extreme obese population (BMI >40 kg/m²) remains sparse (Leeds, 2014; NICE, 2014). Much of the evidence in the latter population comes from people using VLEDs for 2–6 weeks prior to bariatric surgery to help rapidly reduce liver fat and volume – the so-called “liver shrinkage diet” (Fris, 2004; Colles et al., 2006; Lewis et al., 2006). Despite this, within clinical practice in the UK, 49 preoperative diets have been observed in current use (Baldry et al., 2014), which raises the question of whether bariatric services should continue using preoperative diets that have no evidence base behind them.

The latest update of the NICE obesity guidelines (CG189; NICE, 2014) reviewed the evidence for using VLCDs in people with a BMI >40 kg/m², which was only briefly addressed in the original 2006 guidelines. NICE now recommends that VLEDs should not routinely be used within clinical practice to manage obesity (defined as BMI >30 kg/m²) and only in people with a clinically assessed need for rapid weight loss, such as those who are seeking fertility services. Additionally, VLEDs should be used in conjunction with a long-term, multicomponent weight management service, including psychological assessment and discussion regarding risks, benefits and possible weight regain after reintroduction of food. VLEDs should only be followed for a maximum of 12 weeks, continuously or intermittently. Interestingly, LEDs (>800 kcal/day) were only briefly mentioned in the 2014 update and were not included in the above review.

Other position statements from the National Obesity Forum (NOF, 2010) and the British Dietetic Association’s obesity special interest group, Dietitians in Obesity Management UK (DOM UK, 2007) further add to these recommendations, although neither statement currently supports every recommendation made by NICE. Within both statements, VLEDs can be considered for people with a BMI ≥30 kg/m², and medical supervision is needed for those with obesity-related comorbidities. In addition, NOF suggest no time limit or age limit, as long as monitoring and medical supervision are included, and they suggest that GP approval is not required for all patients, provided that adequately trained staff delivers the programme.

The issue of weight cycling was highlighted in the NICE guidelines, as epidemiological studies indicate that this increases the risk of morbidity and mortality (Lissner et al., 1991), as was the potential psychological effect of weight regain. However, identifying the difference between intentional and unintentional weight loss is difficult, and in a recent systematic review it was concluded that there was no causal association of weight cycling with early mortality or morbidity, with evidence being sparse regarding any negative impact (Mehta et al., 2014).

As studies are often conducted in diverse populations and countries, the implementation of weight loss interventions, including those utilising LEDs, within clinical practice can be challenging. Two UK studies observing the use of VLEDs and LEDs in commercial and clinical environments have recently been published. In a feasibility study conducted within primary care, investigators from the Counterweight Programme used an LED in patients with a BMI of ≥40 kg/m² (Lean et al., 2013). With structured food reintroduction and weight maintenance, with optional orlistat in the first year of treatment, the participants (68 completers, out of 91 enrolled) recorded mean weight losses of 12.4±11.4 kg, with 30% achieving ≥15 kg of weight loss at 12 months. Importantly, it was also observed...
that the programme might be cost-effective within the primary care setting. In further support of this, a retrospective analysis between 2007 and 2010 of 5965 participants commencing a commercial VLED programme, with additional behaviour change therapy, demonstrated a mean weight loss of 18±11.4 kg and 12.9±10 kg after 1 year and 3 years, respectively (Rolland et al, 2014). While both of these studies had limitations, including the lack of randomisation, selection bias, and significant drop-out rates, they show that, in motivated patients, an LED approach combined with behaviour change therapy can successfully achieve clinically significant, maintainable weight loss.

Another clear advantage of formula diets is their ability to remove food from the daily decision-making process (Leeds, 2014) while providing a person with a known amount of calories (Purcell et al, 2014). This can allow participants to focus on introspectively looking at their relationship with food, identifying the difference between emotional and physical hunger and gaining skills to aid long-term weight maintenance.

Low-energy formula diets in people with type 2 diabetes, cardiovascular disease and other obesity-related comorbidities

Significant long-term improvements in weight-related comorbidities have been seen following VLEDs (Tsai and Wadden, 2006). Current evidence with a minimum follow-up of 12 months suggests that weight loss and improvements in waist circumference, blood pressure and lipid profiles occur following a VLED (Mulholland et al, 2012). With evidence that the calorie restriction immediately following bariatric surgery is pivotal to the observed improvements in glucose homeostasis (Lips et al, 2014; Plourde et al, 2014), and that ectopic fat (particularly within the liver and pancreas) is a key part of the aetiology of type 2 diabetes (Taylor, 2013), there is now mounting evidence for the effective use of LEDs in people with type 2 diabetes. This was supported by a small pilot study of 11 people with type 2 diabetes who underwent a VLED for 8 weeks (Lim et al, 2011). These participants showed normalised hepatic insulin sensitivity and beta-cell function, which was directly associated with reduced triacylglycerol levels in the liver and pancreas, respectively. Moreover, in another study of the same diet in 29 people with type 2 diabetes, of the 14 participants with long-duration diabetes (>8 years), fasting plasma glucose levels normalised in 50% (Steven and Taylor, 2015). These findings suggest that acute energy restriction could reverse the abnormalities typical to type 2 diabetes.

Further studies have looked at LEDs in people with type 2 diabetes receiving either oral hypoglycaemic agents or insulin, showing significant improvements in weight, glycaemic control, cardiovascular disease and quality of life (Paisey et al, 2002; Dhindra et al, 2003; Snel et al, 2012a; 2012b; 2012c). However, methodological limitations, including lack of control groups, selection bias and only reporting completers, affect the generalisability of these findings and hamper translation to best clinical practice.

Oral hypoglycaemic medications and insulin require significant dose reductions following initiation of an LED or VLED, in order to reduce the risk of hypoglycaemia. Haslam et al (2010) recommend gradual titration of dietary energy intakes down to the target intake, in order to avoid rapid changes in insulin dose, and a possible pre-emptive reduction of insulin by 25% at commencement of an LED (Haslam et al, 2010). It should also be noted that people with advanced stages of type 2 diabetes might be at risk of hyperglycaemia if all diabetes medications are ceased.

Weight loss has been shown to improve not only insulin resistance but also cardiac function, with the degree of weight loss being key to these improvements (Rider et al, 2009; Jonker et al, 2014). VLEDs reduce both cardiovascular risk and its associated surrogate markers (Mulholland et al, 2012), with a 16-week VLED being associated with decreased myocardial triglyceride content and improved diastolic function (Hammer et al, 2008). Other benefits of formula diets include improvements in psoriasis (Jensen et al, 2014), osteoarthritis (Christensen et al, 2011; 2014) and obstructive sleep apnoea (Johansson et al, 2011). However, it must be appreciated that non-favourable evidence is also present within the literature (Tsai and Wadden, 2006; Mulholland et al, 2012). Clearly, further high-quality research is still required to confirm findings and translate them.
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Attrition

The perceived rate of attrition is a significant deterrent for people considering LEDs. Attrition rates vary depending on the initial intervention and follow-up, with figures ranging between 0% and 52%, and there is very little difference between VLEDs and LEDs (Tsai and Wadden, 2006; Christensen et al, 2011). Drop-outs occur throughout the patient journey, albeit more frequently during the follow-up period (Mulholland et al, 2012), when people potentially regain some of the weight lost. Within the actual diet period, poor compliance, work schedules and dislike of the products commonly feature as reasons for dropping out, while younger participants and those with a higher BMI more often drop out during follow-up (Mulholland et al, 2012). Interestingly, when compared with conventional dietary approaches, meal replacements can aid both compliance and perceived convenience (Noakes et al, 2004).

Side-effects

Table 1 shows the advantages and disadvantages of LEDs. During the initial stages of rapid weight loss with these diets, individuals may experience side-effects such as hair loss, fatigue, dizziness, constipation, acute gout, cold intolerance, headaches, muscle cramps and gallstones (Wadden et al, 1983b; Saris, 2001). In a recent randomized controlled trial, at 8 weeks, compared with LED users, VLED users had a significantly higher incidence of bad breath (35% vs. 22%), intolerance to cold (41% vs. 18%) and flatulence (45% vs. 28%; P<0.05 for all comparisons), with trends towards greater risk of hair loss and dry skin (Christensen et al, 2011). Mirroring previous findings, this study suggested that LEDs have fewer adverse effects than VLEDs, and this should be considered when choosing between the two diets (Rössner and Flaten, 1997).

Patients should also be made aware that acute gallstone events and gout have been reported following significant weight loss (Christensen et al, 2011; Johansson et al, 2011). However, incidences of gallstone disease have mostly been reported in the US, where formula diets contain lower levels of essential fatty acids than in the EU (Saris, 2001).

Side-effects with formula diets are generally mild and easily managed, although, if VLEDs are used unsupervised in high-risk individuals, they may result in serious complications (Wadden et al, 1983b). VLEDs cannot be used with every patient and there are currently several contraindications to their use, including pregnancy, acute kidney disease and gout (Box 1).

The loss of excess lean body mass following LEDs poses several risks (Heymsfield et al, 2014), and lean tissue losses of 14–30% have been reported, depending on the patient population and the inclusion of physical activity in the regimen (Christensen et al, 2011; Snel et al, 2012a). Sufficient amounts of protein and associated carbohydrate are essential to minimise protein turnover and maintain nitrogen balance. Hopefully, with the new EU regulations, loss of lean body mass will continue to be minimised.

Research has suggested that poor diet quality and micronutrient deficiencies are more common in obese individuals compared to normal-weight people (Kimmons et al, 2006; Damms-Machado et al, 2012). With evidence that traditional popular
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weight loss diets have a high likelihood of being micronutrient-deficient (Calton, 2010), theoretically, formula diets that provide 100% of the Daily Reference Intake for healthy adults could help to improve these deficiencies during weight loss. Evidence is variable, suggesting both improvements and further deteriorations in nutritional status in obese individuals who follow a formula diet (Damms-Machado et al, 2012; Christensen et al, 2013). Undoubtedly, further evidence is required.

Conclusion

The use of LEDs has been shown to be effective in producing clinically significant weight loss and, with the addition of weight-loss maintenance strategies, can produce a long-term body weight loss of around 10%, combined with improvements in obesity-related comorbidities. Evidence is now growing for the use of VLEDs within both diabetes and osteoarthritis. Furthermore, the erroneous beliefs that LEDs are unsafe and that the rapid weight loss is not maintained are increasingly being challenged.

At present, it is difficult to recommend best practice regarding LEDs (Mulholland et al, 2012; Johansson et al, 2014). Although higher-quality data have been published more recently, previous papers often only reported data on completers and had significant methodological heterogeneity. This has been reflected by the differing statements from the professional bodies and the fact that NICE (2014) does not yet recommend VLEDs in routine care.

From the current scientific evidence, it appears that LEDs may have a place within weight management and clinical practice; however, if clinicians are to consider them, it is important that the right infrastructure be in place to support the patient, in order to ensure both safety and weight maintenance. With research in this area gaining momentum, the use of LEDs in routine care may indeed change in the future.

Conflicts of interest

The authors have received funding for investigator-initiated research through an educational grant from Cambridge Weight Plan Ltd.

Acknowledgement

Shahrad Taheri receives funding from the Biomedical Research Program (BMRP) at Weill Cornell Medical College in Qatar, supported by the Qatar Foundation, and from the Qatar National Research Fund National Priorities Research Programme (NPRP), grant no. NPRP 8-912-3-192.


Box 1. Contraindications for the use of very-low-energy diets.

- Infants and children.
- Pregnancy and lactating women.
- Unstable cardiac or cerebrovascular disease.
- Acute and chronic renal failure.
- Severe or end-stage liver failure.
- Acute psychiatric disorder.
- Gout.

British Journal of Obesity Volume 1 No 3 2015
Nokia M, Foster PR, Krehg JB, Clifton PM (2014) Meal replacements are as effective as structure-weight loss diets for treating obesity in adults with features of metabolic syndrome. J Nutr 134: 1894–9

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