Obesity Surgery
https://doi.org/10.1007/s11695-019-03916-2

ORIGINAL CONTRIBUTIONS

Improving Compliance with Very Low Energy Diets (VLEDs) Prior to Bariatric Surgery—a Randomised Controlled Trial of Two Formulations

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Abstract

Introduction Preoperative very low energy diets (VLEDs) improve access during bariatric surgery. Compliance with traditional VLED is variable, mainly due to gastrointestinal side effects. Formulite™ is a new formulation of VLED, with higher protein, soluble fibre and probiotics.

Aims To compare traditional VLED (Optifast™) with the new VLED (Formulite™) and assess compliance, weight loss, satisfaction, side effects and surgical access.

Methods This was a randomised double-blinded study involving patients scheduled for bariatric surgery. The primary outcome was compliance, assessed by urinary ketone concentration and proportion of patients in ketosis at 2 weeks. Secondary outcomes were weight loss, satisfaction and patient reported outcomes, gastrointestinal side effects and operative conditions.

Results There were 69 participants: 35 in the Formulite™ group and 34 in the Optifast™ group. Ketosis at 2 weeks was achieved in both groups (88.5% vs 83.3%, Formulite™ vs. Optifast™, $p = 0.602$). Urinary ketones were higher with Formulite™ (1.5 vs 15 mmol/L, $p = 0.030$). Total body weight loss percentage, hunger and operative conditions were similar in both groups. Formulite™ produced less flatulence (score 3 vs 2, $p = 0.010$) and emotional eating (score 2 vs 1, $p = 0.037$); however, Optifast™ ranked higher in terms of taste (score 4 vs 3, $p = 0.001$) and overall satisfaction (score 5 vs 7, $p = 0.011$).

Conclusions Compliance over 2 weeks was high in both VLEDs with most subjects achieving ketosis. Overall satisfaction was moderately high, although variable. Whilst Formulite™ is a viable alternative to Optifast™, better formulations of VLED that addresses key adverse effects, whilst achieving ketosis, would be of significant value.

Keywords Very low energy diet · Bariatric surgery · Compliance

Introduction

Preoperative weight loss with a short-term very low energy diet (VLED) reduces risk in bariatric surgery. Weight loss prior to bariatric procedures has been shown to reduce liver volume and visceral adiposity [1], thereby improving surgical access and safety. This translates to shorter operating times, less blood loss and a shorter hospital stay [2].

In addition, preoperative VLED appears to improve metabolic status, reduce perioperative anaesthetic risk and postoperative complications [3, 4]. For these reasons, many clinicians request that patients undergo a preoperative weight loss programme for a minimum of 2 weeks [5].

Whilst clinicians perceive a clear benefit from preoperative weight loss, patients often struggle to comply [4, 6]. In a previous study, compliance with current VLED was 86% at 2 weeks. Of those patients who were unable to comply, 80% stated this was due to taste and gastrointestinal (GI) side effects, such as abdominal bloating, diarrhoea and constipation [1].

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Published online: 21 May 2019

Formulite™ is a new VLED that aims to retain the benefit of traditional VLED, whilst reducing unwanted GI side effects. Similar to previous VLED, it induces ketosis, thereby decreasing hunger and producing rapid weight loss. However, there are several differences in the formulation (Table 1) [7]. Compared to traditional VLED such as Optifast™, Formulite has a higher protein content, with lower amounts of carbohydrate and sugar. Furthermore, it contains increased fibre, digestive enzymes and probiotics. These changes seek to reduce unwanted side effects, making the VLED more acceptable and, therefore, improving compliance.

We sought to compare Formulite™ with Optifast™ in patients undergoing bariatric surgery. We hypothesised that patient satisfaction would be higher, and therefore, compliance with the preoperative weight loss programme would be improved compared to traditional VLED (e.g. Optifast™).

The primary aim of this study was to determine whether Formulite™ resulted in improved patient compliance, as measured by urinary ketone concentration. We secondarily aimed to investigate the differences in preoperative weight loss, patient satisfaction, patient-reported outcomes, gastrointestinal side effects and surgical conditions with the use of both products.

Methods

Ethics approval was obtained from the Avenue Ethics Committee (ref no. 210). The trial was registered with the Australian Clinical Trials Register (ACTRN 12616001091493 at www.anzctr.org.au). All participants provided written informed consent.

We undertook a double-blinded, randomised controlled trial in obese patients who were scheduled for bariatric surgery by three surgeons affiliated with the Centre for Bariatric Surgery in Melbourne. The CONSORT checklist was used to guide reporting of this study.

Table 1 Differences between Formulite™ and Optifast™

	Formulite™	Optifast™
Serving size (g)	55	54
Calories (cal/kJ)	204/853	207/870
Protein (g)	35.4	17.5
Carbohydrate (g)	8.1	22.5
Sugar (g)	3.6	17.8
Fat (g)	3.4	4.5
Dietary fibre (g)	4.95	3.6
Sodium (mg)	178	220
Vitamins and minerals	Yes	Yes
Probiotics	Yes	No

Participants

Inclusion criteria were patients scheduled for bariatric surgery. Patients were excluded from this study if they would not accept the randomisation process; had a history of previous bariatric surgery; had medical issues considered a contraindication to the application of either arm of the study such as lactose intolerance, or significant medical comorbidities.

Baseline data were collected either at the time of the patient booking for surgery or within that week in a clinical setting. Data on the day of surgery was collected at the hospital where surgery was performed.

Interventions

There were two arms to this trial, with patients being randomised to 2 weeks of Formulite™ (intervention—higher protein, higher fibre) or Optifast™ (standard care). The treating practitioner and patients were unaware of programme assignment.

Meal replacements were provided by the manufacturer of Formulite™. Optifast™ was purchased using departmental funding. Both were repackaged in identical plain packs. Sufficient product for 2 weeks was provided to each patient at the initial visit (2400 g). Patients commenced the meal replacement programme 2 weeks prior to their scheduled surgery.

Data Collection

Baseline Measures

At baseline, all participating patients were assessed for weight, height, blood pressure, neck circumference, waist circumference and hip circumference. The presence of type II diabetes (T2DM), hypercholesterolaemia, hypertension and reflux were specifically noted. Patients were asked to complete a quality of life (SF36) and gastrointestinal (GI) symptoms questionnaire.

Outcome Measures

The *primary outcome measure* was compliance rate as defined by urinary ketone concentration and proportion of patients achieving ketosis. After the first week of a VLED, an increase in the urinary excretion of ketoacids occurs subsequent to increased fat catabolism; therefore, the presence of at least traces of ketones in the urine can be considered to indicate net lipolysis and dietary adherence. Urine samples were collected on the day of surgery (2 weeks after starting VLED) for measurement of urinary ketones. Urinary ketone measurements were obtained using ChoiceLine 10 urinalysis urine test strips (Roche Diagnostics GmbH).

Secondary outcome measures included weight loss achieved, overall satisfaction, patient-reported outcomes, gastrointestinal symptoms and hunger, and operating conditions (effects of liver volume) as assessed by the treating surgeon.

The baseline weight was defined as the weight documented prior to beginning preoperative VLED. Excess weight loss (EWL) was defined as the percentage weight lost from the weight above ideal (defined as BMI 25) at baseline. Percentage total body weight loss (TBWL) was defined as the percentage of absolute weight lost.

Qualitative methods were used to measure product side effects and acceptability across the domains of overall satisfaction, patient-reported outcomes (taste, emotional eating, social eating, change in concentration and difficulty sleeping), bothersome gastrointestinal side effects and hunger, and operative conditions as evaluated by operating surgeons. Patients were assessed at the completion of the 2-week trial using previously published protocols [1], rating six factors on a 5-point Likert scale. Median group ratings for each factor at baseline and 2 weeks were compared.

Sample Size Calculation

Compliance with current VLED has been reported as 86% at 2 weeks [1]. Eighty percent of patients who failed to comply stated this was due to taste and GI side effects. We therefore anticipated that Formulite™ would ameliorate these issues and achieve a 97 ± 10% compliance. Assuming an alpha of 0.05 and power of 0.8, with two independent groups, ratio of 1:1, 28 patients were required for each arm of the study. Based on our previous experiences, we anticipated a 20% dropout rate. Therefore, we aimed to recruit 35 patients per arm, for a total of 70 patients.

Randomisation

The random assignment of eligible patients was computer generated by the Monash University School of Public Health and Preventative Medicine (SPHPM) data centre which employs this type of system for all major trials. A telephone-based system was established, which allowed a check of patent eligibility and randomisation only proceeded if the patient meets the criteria. Randomisation was clustered into blocks of between 6 and 8 to ensure even distribution.

Blinding

Patients, treating surgeons and researchers were blinded to the programme assignment. The Trial coordinator was aware of programme assignment after completion of data collection.

Statistical Methods

Continuous parametric variables were presented as mean ± standard deviation (SD) and compared using unpaired two-tailed Student's *t* test. Continuous non-parametric variables were represented as median and interquartile range (IQR) and compared using Mann–Whitney *U* test. Binary outcomes were represented as numbers and percentages and compared using chi-squared test. Aggregated scores of participants' response to VLED and hunger at different meal times were obtained by calculating the difference between baseline and at completion of VLED. These results were then compared between the two groups using Mann–Whitney *U* test. Product acceptance including taste, satisfaction as well as the surgeons' perception of operative conditions were measured using Mann–Whitney *U* test.

Results were considered significant if $p < 0.05$. Analysis was conducted using SPSS Statistics (version 25; SPSS, Chicago, IL, USA).

Results

Baseline Characteristics

Baseline characteristics of participants are presented in Table 2. Sixty-nine participants were included in the study, of whom 35 were randomised to receive Formulite™ and 34 to receive

Table 2 Baseline characteristics, comparing the Formulite™ group and the Optifast™ group

Variables	Formulite™	Optifast™	*p* value
n	35	34	
Age (years)	41.2 ± 12.9	40.7 ± 13.6	0.886
Female gender (*n*)	31 (88.6%)	32 (94.1%)	0.382
Baseline measurements			
Weight (kg)	119.9 ± 21.7	120.4 ± 20.5	0.793
Body mass index (BMI, kg/m^2)	42.2 ± 19.6	43.0 ± 8.1	0.660
Excess weight (kg)	46.3 ± 18.4	50.2 ± 16.9	0.450
Neck circumference (cm)	46.8 ± 22.7	41.1 ± 3.8	0.152
Waist circumference (cm)	123.0 ± 14.7	122.7 ± 14.3	0.931
Hip circumference (cm)	129.0 ± 25.1	133.8 ± 24.9	0.431
Systolic blood pressure (mmHg)	138.5 ± 15.3	134.4 ± 16.5	0.327
Diastolic blood pressure (mmHg)	86.4 ± 9.6	82.5 ± 10.8	0.158
Comorbidities			
Diabetes	1 (2.9%)	3 (8.8%)	0.289
Hypertension	5 (13.2%)	9 (26.5%)	0.208
Hypercholesterolaemia	5 (13.2%)	9 (26.5%)	0.208
Gastro-oesophageal reflux	8 (13.2%)	11 (32.4%)	0.377

Student's *t* test for continuous data and chi-squared test for categorical data, unless otherwise specified

Optifast™. Baseline characteristics of both groups were well-matched for age, gender, baseline weight and BMI, baseline neck, waist, hip measurements, as well as comorbidities.

Primary Outcomes

Primary outcomes measured are shown in Table 3 and Fig. 1. Urinary ketones at completion were higher in the Formulite™ group compared to the Optifast™ group (3.0 ± 3.7 vs 1.2 ± 1.3, $p = 0.023$) (Fig. 1a). Formulite™ resulted in ketosis in 88.5% of participants at completion compared to 83.3% in the Optifast™ group ($p = 0.602$) (Table 4).

Secondary Outcomes

Weight Loss Outcomes

Overall, there was no statistically significant difference between the two groups in terms of weight loss and physical measurements at completion (Fig. 2a). Total body weight loss percentage in the Formulite™ group was 4.4 ± 2.3% compared to 3.5 ± 1.9% in the Optifast™ group ($p = 0.099$). Urinary ketones at completion positively correlated with weight loss (Pearson correlation $r = 0.417$, $p = 0.002$) and TBWL (Pearson correlation $r = 0.337$, $p = 0.017$) (Fig. 2b). Participants in both groups who were in ketosis achieved greater weight loss (TBWL Formulite™ group with ketone positive 4.84 ± 2.15 kg vs ketone negative 1.94 ± 1.45 kg, $p = 0.034$; TBWL Optifast™ group with ketone positive mean 3.85 ± 1.68 kg vs ketone negative 1.38 ± 2.7 kg).

Overall Satisfaction

Overall participant satisfaction was higher in the Optifast™ group (7 out of 10 (5–8) vs 5 out of 10 (2–7), $p = 0.011$). Of note, a small subset of participants was very unsatisfied with Formulite™ (Fig. 3).

Patient-Reported Outcomes

When comparing the participants' taste rating (Fig. 2c), Optifast™ was superior to Formulite™ (score of 4 out of 10 (3–4) vs 3 out of 10 (2–4), $p < 0.001$). Emotional eating

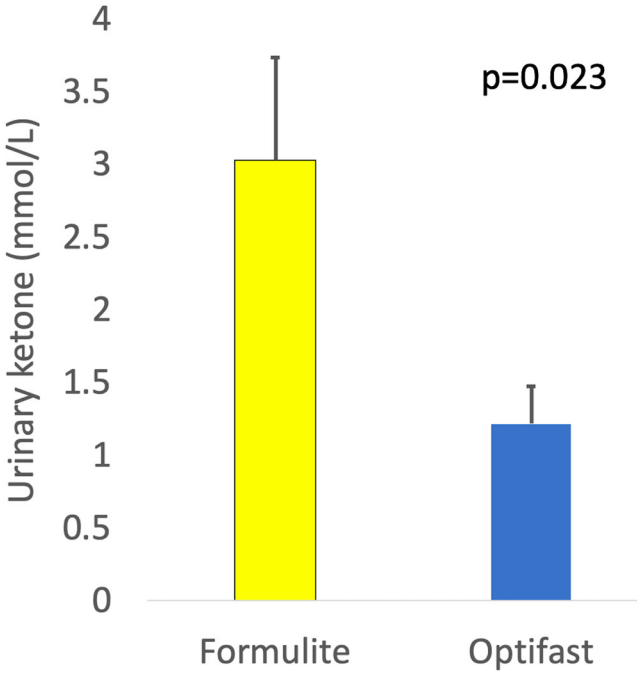

Fig. 1 Primary outcomes—urinary ketones at completion, comparing Formulite™ group and Optifast™ group

appeared to be increased in both groups, more so in the Optifast™ group (positive increase of 2.0 (1.0–3.0) vs 1.0 (0.0–2.0), $p = 0.037$) (Fig. 2d). There was no statistically significant difference with difficulty in sleeping (Fig. 2d). Changes in concentration (score of 3.0 (3.0–4.0) vs 3.0 (3.0–3.3), $p = 0.06$) and social eating (score of 5.0 (4.8–5.0) vs 5.0 (4.0–5.0), $p = 0.07$) whilst on either Formulite™ or Optifast™ did not reach statistical significance.

Bothersome Gastrointestinal Side Effects and Hunger

There was no statistically significant difference in the hunger rating at different meal times (Fig. 2e). In terms of GI side effects, Formulite™ produced less flatulence compared to Optifast™ (3.0 (1.0–3.0) vs 2.0 (2.0–3.0), $p = 0.010$) (Fig. 2g). There was no statistically significant difference between the two groups in terms of participants' perception of changes in nausea/vomiting, bowel function, bloating, abdominal pain, reflux or halitosis, seen in Fig. 2f.

Table 3 Primary outcomes

Variables	Formulite™	Optifast™	*p* value
n	35	34	
Proportion of patients who achieved ketosis (%)	88.5	83.3	0.602
Urine ketone concentration at 2 weeks (mmol/L)	3.0 ± 3.7	1.2 ± 1.3	0.023
Weight	114.4 ± 20.3	116.2 ± 20.1	0.709
Body mass index (BMI)	40.4 ± 5.5	41.2 ± 6.8	0.659

Students *t* test for continuous data and chi-squared test for categorical data, unless otherwise specified

Table 4 Secondary outcomes—weight and body measurements at completion

Variables	Formulite™	Optifast™	*p* value
Weight loss (kg)	5.4 ± 3.5	4.2 ± 2.3	0.105
Total body weight loss (%)	4.4 ± 2.3	3.5 ± 1.9	0.099
Post-VLED measurements			
Neck circumference (cm)	40.2 ± 4.1	40.2 ± 3.1	0.991
Waist circumference (cm)	119.5 ± 13.9	122.2 ± 15.5	0.451
Hip circumference (cm)	130.3 ± 10.3	132.4 ± 12.6	0.476
Systolic blood pressure (mmHg)	14.9 ± 16.8	131.5 ± 17.4	0.436
Diastolic blood pressure (mmHg)	77.7 ± 9.5	78.2 ± 13.8	0.842
Differences between measurement pre- and post-VLED			
Neck circumference (cm)	2.4 ± 6.6	1.0 ± 2.0	0.272
Waist circumference (cm)	3.3 ± 6.9	0.8 ± 6.2	0.126
Hip circumference (cm)	3.0 ± 5.2	5.1 ± 5.6	0.140
Systolic blood pressure (mmHg)	3.9 ± 20.1	3.3 ± 18.4	0.913
Diastolic blood pressure (mmHg)	11.0 ± 18.4	6.5 ± 9.9	0.266

Student's *t* test for continuous data and chi-squared test for categorical data, unless otherwise specified

Operative Conditions

There was also no statistically significant difference between the two groups in terms of the treating surgeons' perception of ease of surgery due to liver volume after completion of VLED (Fig. 2h).

Discussion

We conducted a randomised blinded study comparing a new VLED (Formulite™) with a standard VLED (Optifast™) for 2 weeks in obese patients prior to bariatric surgery. We aimed to primarily assess compliance, and secondarily, to assess

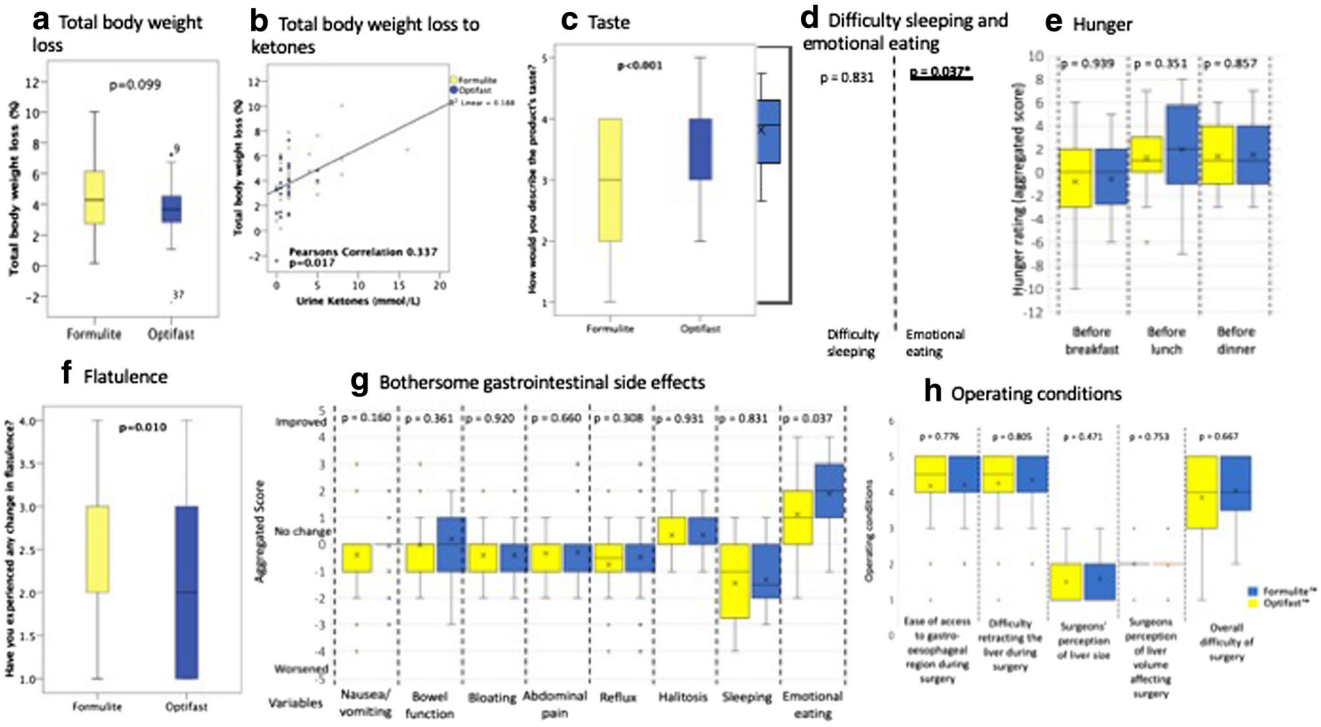

Fig. 2 Secondary outcomes compared between Formulite™ and Optifast™ groups. **a** Total body weight loss percentage (TBWL). **b** Correlation between urinary ketones and TBWL. **c** Taste. **d** Difficulty sleeping and emotional eating. **e** Aggregated scores of participants' perception of hunger according to time of meals. **f** Change in flatulence. **g** Aggregated scores of bothersome gastrointestinal side effects. **h** Surgeon's perception of operating conditions

Fig. 3 Secondary outcome compared between Formulite™ and Optifast™ groups—overall satisfaction

gastrointestinal side effects, satisfaction, patient-reported outcomes and surgeon's perception of operative conditions. Formulite™ was formulated with lower sugar and carbohydrate, higher protein and fibre, as well as the addition of probiotic and digestive enzymes. This composition aimed to address the drawbacks of the standard VLED formulation and therefore improve compliance.

Urinary ketones measured at 2 weeks were used as an objective measure of adherence to the very low-calorie regime. Urinary ketones indicated lipolysis and ketosis, induced by dietary adherence to VLED and low caloric intake. We found higher average urinary ketone concentration in those on Formulite™ compared to Optifast™. However, both groups had good rates of ketosis, with more than 80% of participants in both groups found to be in ketosis on the day of surgery. Furthermore, there was positive correlation between urinary ketosis and total body weight loss in both groups, strengthening its correlation with compliance. This reflected good compliance regardless of product used.

In our study, there was no difference in weight loss between the two groups; however, this study was not powered to find the differences in weight loss between Formulite™ and Optifast™ within 2 weeks. Magnitude of weight loss could be an important consideration for future endeavours, particularly if longer courses of preoperative weigh loss diet are prescribed. Optimal constitution of preoperative diets is unknown. For weight loss in general a focus on high protein, low calorie formulations appear supported by evidence. Four systematic reviews have assessed the impact of high protein diets on weight loss [8–11]. Three of these showed better weight control with a high protein diet involving a 5–10% increase in protein constituent [8–10]. In a large multicentre randomised controlled trial comparing five types of low calorie diet, a high protein diet was associated with the least weight regain after 26 weeks [12].

The new VLED formulation also contained 1.4 g more fibre per meal. Fibre intake had been associated with improved gastrointestinal symptoms in patients with irritable bowel syndrome in two recent meta-analyses [13, 14]. In this study, Formulite™ was associated with less flatulence than Optifast™, although this observation was statistically significant, the magnitude of difference (3 vs 2) was small. This outcome could be explained by the additional fibre intake acquired with the new formulation, similar to the effect seen after the fibre intake increment in irritable bowel syndrome.

Whilst most patient-reported outcome measures were similar between the two VLEDs, there were key differences. Participants rated the taste profile of Optifast™ as better and

were more satisfied overall with the product. A small subset of participants was significantly unsatisfied with Formulite™. Optifast™ was, however, associated with increased emotional eating. This finding has previously been reported during a study that used a 12 week Optifast™ course by Colles et al. [1]. There were no differences in other gastrointestinal side effects, sleeping, emotional eating and hunger ratings between the two cohorts.

There were no differences in surgeon perception of the operative difficulty between products used. The use of VLED preoperatively has previously been associated with preoperative weight loss, reduction of liver volume as well as a surgeon's perceived difficulty of conducting a bariatric procedure. Whilst this finding was reassuring, the nature of the patient population probably makes the study underpowered to detect clinically significant differences. Multiple studies have demonstrated the effectiveness of VLED in weight reduction preoperatively [1, 4, 5, 15, 16]. Alami et al. [2] quoted a reduction in operative time with 10% weight loss prior to gastric bypass; however, this was not associated with differences in major complication rate or conversion rate. In addition, VLED were associated with preoperative reduction in liver volume and better exposure of the hiatal region, contributing to a lower perceived overall complexity [1, 2].

The strength of this study rested on the study design and randomisation design that allowed for comparable participants groups with similar baseline characteristics and physical measurements. Secondly, this study also measured factors that have clinical significance for surgeons and patients in terms of compliance rate, patients' satisfaction and factors influencing compliance including potential side effects contributing to compliance. It also measured the surgeon's perception of liver size and ease of surgery, which was the main reason for preoperative commencement of VLED prior to bariatric surgery.

There were a number of limitations of the study. Firstly, the short duration of 2 weeks did not allow for meaningful observation in weight change post-VLED. The second disadvantage was the study did not consider meals or snacks consumed apart from VLED, which may influence compliance and weight change observed as well as other patient-reported outcomes.

Future directions could include a study with a longer-term observational period and more subjects with a complete dietary diary. Other measures in a future study could include individual energy requirement and metabolic serum markers to comprehensively profile weight and metabolic change as well as patient perceptions and compliance. This is of particular significance given the differences in satisfaction with product and it would be of importance to determine if this were more significant with a longer-term treatment duration. A larger study would be better powered to evaluate the significance of differences observed in patient reported outcome measures such as flatulence and the higher concentration of urinary ketones noted in the formulite group. Pre-VLED and post-VLED liver size measurement with ultrasound or MRI may be of benefit to objectively measure the effect of different VLED's on liver size and visceral adiposity.

This study showed high level of compliance with both VLEDs, over a 2-week period, as measured by the high proportion of subjects achieving measurable ketosis in both groups (88% and 90%) and achieved weight loss in both groups. Total urinary ketones were higher in the Formulite™ group, although this did not translate to higher weight loss or surgeons' perception of ease of operating. Overall satisfaction was higher in the Optifast™ group, largely attributable to a small subset in the Formulite™ group who found it difficult to tolerate. Formulite™ resulted in less bothersome gastrointestinal side effects such as flatulence and resulted in less emotional eating than the standard formulation, however, had a poorer taste rating.

This study also highlights that the use of preoperative diets prior to bariatric surgery is an area requiring significant further research. Some studies informing practice are now dated (> 10 years) and are likely representative of a different laparoscopic era. Furthermore, prospective trials have reported variable outcomes. It remains unclear whether routine use of preoperative diets genuinely reduce operative times, improve intraoperative safety and reduce the risk the risk of postoperative complications. We feel it is likely that presently in selected subsets of patients, genuine advantages will be provided by use of preoperative weight loss regimes; however, prospective trials relevant to current practice are required.

Overall, this study had demonstrated that Formulite™ was a tolerable, viable alternative preoperative VLED. Our data has highlighted the ongoing need to develop formulations able to achieve ketosis with limited bothersome side effects and better overall patient satisfaction.

Compliance with Ethical Standards

Ethical Statement Ethics approval was obtained from the Avenue Ethics Committee (ref no. 210). The trial was registered with the Australian Clinical Trials Register (ACTRN 12616001091493 at www.anzctr.org.au).

Consent Statement All participants provided written informed consent.

Conflict of Interest The product Formulite™ was donated by the manufacturer for the purpose of this study.

Author 1: no conflicts of interest to declare.
Author 2: no conflicts of interest to declare.
Author 3: no conflicts of interest to declare.
Author 4: no conflicts of interest to declare.
Author 5: no conflicts of interest to declare.
Author 6: received a grant from the NHMRC, outside the submitted work.
Author 7: received grants from Johnson and Johnson, grants from Medtronic, grants from GORE, personal fees from GORE, grants from Applied Medical, grants from Apollo Endosurgery, grants and personal fees from Novo Nordisc, personal fees from Merck Sharpe and Dohme, outside the submitted work.

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