Effects of short-term energy restriction on liver lipid content and inflammatory status in severely obese adults: Results of a randomized controlled trial using 2 dietary approaches

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Short-term very-low-energy diets (VLEDs) are used in clinical practice prior to bariatric surgery, but regimens vary and outcomes of a short intervention are unclear. We examined the effect of 2 VLEDs, a food-based diet (FD) and a meal-replacement plan (MRP; LighterLife UK Limited, Harlow, UK), over the course of 2 weeks in a randomized controlled trial. We collected clinical and anthropometric data, fasting blood samples, and dietary evaluation questionnaires. Surgeons took liver biopsies and made a visual assessment of the liver. We enrolled 60 participants of whom 54 completed the study (FD, n = 26; MRP, n = 28). Baseline demographic features, reported energy intake, dietary evaluation and liver histology were similar in the 2 groups. Both diets induced significant weight loss. Perceived difficulty of surgery correlated significantly with the degree of steatosis on histology. There were reductions in the circulating inflammatory mediators C-reactive protein, fetuin-A and interleukin-6 between baseline (pre-diet) and post-diet. The diets achieved similar weight loss and reduction in inflammatory biomarkers. There were no significant differences in perceived operative difficulty or between patients’ evaluation of diet satisfaction, ease of use or hunger frequency. Non-alcoholic fatty liver disease histology assessments post-diet were also not significantly different between diets. The results of this study show the effectiveness of short-term VLEDs and energy restriction, irrespective of macronutrient composition, although the small sample size precluded detection of subtle differences between interventions.

KEYWORDS
bariatric, energy restriction, NAFLD, preoperative, VLED

1 | INTRODUCTION

Ectopic lipid accumulation is a common factor underlying non-alcoholic fatty liver disease (NAFLD), insulin resistance and Type 2 diabetes.1 Metabolic dysfunction is linked to pro-inflammatory mediators such as interleukin-6 (IL-6), fetuin-A and C-reactive protein (CRP), which also contribute to progression to inflammatory non-alcoholic steatohepatitis.2–4

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An energy-restricted diet is used prior to bariatric surgery to facilitate the laparoscopic approach to surgery via a reduction in liver size and improved liver flexibility, by reducing stores of lipid, which enables access to the upper stomach and oesophagus. In practice, this is achieved with the use of a short-term preoperative very-low-energy diet (VLED), or "liver-reducing" diet. Our survey of current practice in 2013 found significant variability in the form, duration and application of the preoperative diet used.

Although weight loss via a VLED is associated with reversal of the obesity-related complications through a reduction of ectopic lipid deposits, there is limited evidence with regard to the effects of the different pre-surgery VLEDs on outcomes related to liver histology, inflammatory markers or on the effectiveness of VLEDs with regard to perceived operative difficulty. The aim of the present study, therefore, was to examine the outcomes of 2 commonly used VLED regimens in severely obese adults before they underwent bariatric surgery. Our primary outcome was liver histology post-diet, with secondary outcomes including weight loss achieved, circulating inflammatory markers before and after the VLED, and peri-operative visual assessment of the liver for perceived difficulty of surgery. We also asked participants to evaluate the diets.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was registered at http://www.isrctn.com/ (registration number: ISRCTN65605485).

We conducted the present randomized controlled trial (RCT) between May 2012 and June 2014. Patients were eligible if they had a body mass index (BMI) >40 kg/m² and had been accepted into the bariatric surgical programme at Derby Hospitals NHS Foundation Trust after discussion by the bariatric surgery multidisciplinary team. Participant exclusion criteria included: age <18 years; secondary NAFLD; type 2 diabetes treated by medication other than biguanides; excess alcohol intake; pregnancy; and exclusions linked to application of a restrictive dietary regime.

Participants were randomly allocated to receive a VLED of 800 kcal/d for 2 weeks preoperatively, in the form of either the Derby Teaching Hospitals NHS Foundation Trust standard pre-bariatric surgery food-based diet (FD) or a meal-replacement plan (MRP) diet using LighterLife nutritional supplements (LighterLife UK Limited, Harlow, UK). Block randomization was used with matched pairs, for gender and diabetes status. The participants and study team who supplied the dietary information to participants, were not blinded to the intervention.

2.2 | Sampling and data collection

Clinical and anthropometric data were collected during visits and from patients' notes. A pre-intervention fasting blood test was carried out, and weight and height were measured at the time of the standard preoperative appointment. On completion of the diet, participants completed a short qualitative evaluation. Participants were weighed post-diet on the morning of their bariatric surgery. When the participant was cannulated for anaesthesia, a further fasting blood sample was taken. Intra-operatively a liver biopsy was taken and the surgeon completed a visual assessment of perceived operative difficulty.

2.3 | Outcome measures

The primary outcome was histological assessment of a liver biopsy performed at the time of bariatric surgery (post-diet). Secondary outcomes were change in total body weight (pre- to post-diet), circulating inflammatory markers (pre- to post-diet), peri-operative visual assessment of the liver for perceived difficulty of surgery and evaluation of dietary approach (post-diet).

2.4 | Sample size

The sample size was based on an estimation of the difference in liver lipids after following the FD or MRP. For 80% power (at P = .05) 98 participants would need to be randomized (49 to each arm) to see a statistically significant difference in the level of steatosis (INSTAT GRAPH PAD V2.0 software).

2.5 | Statistical methods

The data were analysed using IBM SPSS Statistics for Windows version 22 (IBM Corporation). Two-tailed non-parametric statistical tests were used: Wilcoxon signed rank test, Spearman's Rho, Mann-Whitney U-test and Kendall's Tau C-test. P values <.05 were taken to indicate statistical significance. Bonferroni correction for multiple comparisons was carried out where stated.

Further details of methods and data collection can be found in File S1.

3 | RESULTS

A total of 196 potential participants were screened for eligibility over a 25-month period of recruitment, of whom 105 verbally consented to the study. Of these, 60 completed informed consent, were randomized and started the trial, and 54 completed the study. Six participants did not complete the study; 5 because of operations being cancelled and 1 participant was started on insulin. One adverse event and 1 serious adverse event, were reported but were not deemed to be related to the intervention.

3.1 | Baseline data

Participants' baseline data are shown in Table 1. BMI ranged from 41.5 to 66.8 kg/m², with a median of 50.7 kg/m², and 81.5% of the participants were women, which is consistent with the national average for patients undergoing bariatric surgery. Age ranged from 24 to 65 years, with a median of 45 years. There was no significant difference between diet groups demographically or anthropometrically (age: P = .245; BMI: P = .691; gender: P = .568; diabetes status: P = .860).
3.2 | Liver tissue histology

After the intervention, there was no significant difference between the groups with regard to steatosis: 12 of 24 participants in the FD group (50%) and 18 of 28 participants in the MRP group (64%) had histological evidence of steatosis (Table 2). Three of 24 participants in the FD group (12.5%) and 4 of 28 participants in the MRP group (14.3%) had evidence of moderate or severe steatosis (steatosis grades 2-3), while 37% of participants in the FD group, and 39% of participants in the MRP group had evidence of significant portal or periportal fibrosis, but the difference between groups was not statistically significant. No significant difference was found between the 2 diet groups in steatosis grade ($P = .349$), liver cell injury ($P = .567$), portal inflammation ($P = .611$), lobular inflammation ($P = .455$), or fibrosis stage ($P = .605$).

3.3 | Weight change and self-reported intake

The median total body weight loss was 3.6% in the FD group, and 3.4% in the MRP group. Results were not significantly different between diet groups, for body weight loss or percentage weight loss ($P = .993$) or estimated energy intake ($P = .311$), however all macronutrient intakes were significantly different ($P < .001$). Data are median (range) unless stated otherwise.

3.4 | Surgeons’ assessment

In 22 of the 54 cases, a surgeon completed a visual assessment of (1) access to the gastro-oesophageal junction, (2) liver volume and (3) liver rigidity. Increasing perceived difficulty was associated with higher percentages of steatosis (as assessed histologically). There was a correlation between visual assessment by the surgeons and the 3 assessment categories (above). There was no significant difference between diets for the 3 visual analogue assessments: gastric access ($P = .513$), liver volume ($P = .891$) and liver rigidity ($P = .702$).

3.5 | Blood results

Concentrations of CRP and fetuin-A reduced significantly after both diets, IL-6 reduction was not significant.

3.6 | Dietary evaluation

Participants’ self-reported evaluation showed that overall satisfaction with the diets was 92% and 85% (satisfied or very satisfied) and 82%
of participants in the FD group and 93% in the MRP group reported that they found the diet easy to follow. A total of 19% in the FD group and 15% in the MRP group reported always feeling hungry, whereas 8% and 11% respectively never felt hungry. There were no significant differences between evaluation responses for satisfaction, ease of use or hunger frequency between diets. Further results are provided in File S1.

4 | DISCUSSION

This RCT examined 2 energy restrictive dietary regimens aiming for 800 kcal/d for a period of 2 weeks prior to bariatric surgery. We found that both dietary approaches achieved equivalent and significant outcomes. In the 2-week period of intervention, patients in both groups lost ~3.5% of their total body weight, alongside a reduction in CRP and fetuin-A. This reflects an improvement in obesity-related systemic inflammation, the clinical significance of which requires further work to evaluate.

Macronutrient composition between the FD and MRP regimens was significantly different, with 52% of total energy intake from carbohydrate in the FD compared with 38% in the MRP regimen. A previous study showed that a reduced carbohydrate diet with moderate energy restriction leads to significantly more reduction in liver lipids at 48 hours than a higher-carbohydrate diet. The present study showed that when VLED interventions are considered over a period of 2 weeks, both FD and MRP were effective, irrespective of macro-nutrient composition.

The main objective of a preoperative energy restrictive dietary intervention is to improve intra-operative conditions for a laparoscopic surgical procedure. At the time of surgery, we found a lower than expected proportion of patients had histological evidence of NAFLD on liver biopsy and steatosis levels were associated with visual assessment by the surgeons of operative difficulty. Both of the preoperative diets could therefore be reasoned to have enabled surgery, from the perspective of reducing difficulty of the surgery, due to limiting steatosis.

We also observed reduction in the biomarkers of obesity-related systemic inflammatory response. Fetuin-A is an endogenous ligand for Toll-like receptor-4 through which free fatty acids induce inflammatory signalling and insulin resistance. Patients with severe obesity have markedly raised fetuin-A levels. Markers of systemic inflammation, such as CRP, have been found to be determinants of risk for development of diabetes. Although the findings of the present RCT are in line with observations in other studies, in which these markers correlated with measures of obesity and reductions occurred with significant weight loss, the majority of these observations were made after longer periods of energy restriction and greater weight loss. The novelty of the present findings is that the observed reduction in pro-inflammatory cytokines occurred after only 2 weeks and with 3.5% weight loss.

The main limitation to the present study is the failure to reach the desired sample size; however, the results for NAFLD were similar to observations elsewhere after an energy restrictive diet when applied in the severely obese population. In addition, we were unable to obtain liver biopsies or to perform non-invasive estimation of hepatic lipid content using MRI both prior to and after the interventions, which would have allowed a more conclusive outcome appraisal. Randomization appears to have been effective, however, and no significant differences in demographic or anthropometric profile were observed between the 2 groups at baseline.

In conclusion, the present results indicate that energy intake of 715 kcal/d for 2 weeks improves operative conditions regardless of the macronutrient composition of the preoperative diet. Participants were satisfied with the VLEDs, which they also found easy to use. The fatty liver disease we found was in line with similar studies and is suggestive of an effect of both diets in reducing liver lipid concentrations. Reductions in inflammatory biomarkers require further investigation. We were unable to demonstrate a difference in either case between diets, and the small sample size may have precluded detection of subtle differences.

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Author contributions

G. P. A., A. B. and I. M. conceived and designed the study, I. M., P. L. and I. I. supported the organization of the study and acquisition of data/samples. P. K. completed histological assessment of liver biopsies. E. B. collected, processed and analysed all data/samples. All authors contributed to interpretation of data and the drafting of the article. There are no competing interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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