Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging[1–3]

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ABSTRACT

Background: A very-low-energy diet (VLED) can result in substantial, rapid weight loss and is increasingly prescribed before obesity surgery to minimize risk and difficulty by reducing liver size and abdominal adiposity. Despite its growing popularity, a VLED in this setting has received little attention.

Objective: The aim of this study was to investigate the efficacy and acceptability of a preoperative VLED.

Design: In a prospective observational study, 32 subjects ($n = 19$ men and 13 women) with a mean (±SD) age of 47.5 ± 8.3 y and a body mass index (in kg/m^2) of 47.3 ± 5.3 consumed a VLED for 12 wk. Primary outcomes included changes in liver volume (LV) and in visceral and subcutaneous adipose tissue (VAT/SAT). Changes in body weight, anthropometric measures, and biochemical variables were also recorded, and compliance with, acceptability of, and side effects of treatment were assessed. Changes in LV and VAT/SAT area were measured by computed tomography and magnetic resonance imaging at baseline and weeks 2, 4, 8, and 12.

Results: Mean (±SD) LV, VAT/SAT, and body weight decreased significantly ($P < 0.001$ for all). The degree of LV reduction was directly related to the reduction in relative body weight ($r = 0.54$, $P = 0.001$) and initial LV ($r = 0.43$, $P = 0.015$). Eighty percent of the reduction in LV occurred between weeks 0 and 2 ($P < 0.001$). Reductions in body weight and VAT were uniform over the 12-wk period. Attrition was 14%. Acceptability was adequate but waned over time, and mild transitory side effects occurred.

Conclusions: Given the observed early reduction in LV and the progressive reduction in VAT, we suggest that the minimum duration for a preoperative VLED be 2 wk. Ideally, the duration should be 6 wk to achieve maximal LV reduction and significant reductions in VAT and body weight without compromising compliance and acceptability. *Am J Clin Nutr* 2006;84:304–11.

KEY WORDS Severe obesity, fatty liver, very-low-energy diet, VLED, weight loss, surgery, laparoscopy, body composition

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), characterized predominantly by steatosis, and nonalcoholic steatohepatitis (NASH) with additional lobular inflammation and fibrosis are strongly related to obesity and metabolic and inflammatory features of the metabolic syndrome (1, 2). Prevalence estimates of NAFLD vary; however, it has been suggested that one-third of persons with NAFLD are severely obese [body mass index (BMI; in kg/m^2) >35] (3), and rates of liver steatosis are predicted to increase, as is the worldwide occurrence of obesity and diabetes (4).

Although NAFLD arises most often without clinical symptoms, an enlarged fatty liver can increase surgical risk and complexity in patients undergoing upper abdominal laparoscopic surgery (5–7). Key elements of the 2 most common obesity surgery procedures in the world today, Roux-en-Y gastric bypass (RYGBP) and the laparoscopic adjustable gastric band (LAGB), require exposure and surgery in the area of the gastroesophageal junction. Hepatomegaly has been cited as the most common cause for conversion to an open procedure from laparoscopic RYGBP (8) and LAGB placement (9). Surgeons at our center estimate that hepatomegaly increases surgical difficulty in ≈10–20% of cases, and excessive omental fat, covering the structures of the left-upper quadrant of the abdomen, provides an additional technical challenge.

Although the etiology of NAFLD is unclear and the most appropriate treatment option has not yet been decided on, weight reduction is a primary aim in the management of NAFLD associated with overweight and obesity (10, 11). Weight loss by obesity surgery (12, 13), low-calorie diets (14), and very-low-energy diets (VLEDs) (15, 16) can reduce weight, liver steatosis, necroinflammatory change, and fibrosis. In the presurgical setting, a VLED provides the benefit of rapid weight loss (17), with no compromise to immune function (18) or wound healing (19), and few side effects (20).

Safe and effective interventions to reduce massive hepatomegaly before laparoscopic surgery should benefit surgeons and patients alike. However, before this practice can be broadly considered, we need good evidence that a clinically relevant reduction in liver size can be achieved. The surgeon is also interested in identifying those at greatest risk so that therapy can, if effective, be focused on those likely to benefit most. Identifying the pattern of liver volume reduction will also guide the optimal time frame for preoperative weight-loss intervention.

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The aims of this study were to investigate the efficacy and acceptability of preoperative weight loss with a VLED. Specifically, we wished to investigate in a severely obese population *1*) the actual changes in liver volume and the pattern of this change during weight loss with a VLED; *2*) the relative change in liver volume, body weight, and visceral and subcutaneous adipose tissue (VAT/SAT) areas; *3*) the anthropometric, clinical, and biochemical risk factors that may predict an enlarged pretreatment liver or predict the total change in liver volume after treatment; and *4*) patient acceptability and compliance and treatment side effects.

SUBJECTS AND METHODS

Patient selection

During May 2004 to July 2005, 37 morbidly obese (BMI > 40) subjects were selected to undergo a 12-wk VLED (Optifast VLCD; Novartis Consumer Health Australasia Pty Ltd, Mulgrave, Australia) intervention before LAGB placement, with the use of the Lap-Band System (Inamed Health, Santa Barbara, CA), at The Avenue Hospital, Melbourne, Australia. The study was approved by the Avenue Hospital Ethics Committee and was in accordance with the Helsinki Declaration of 1975 as revised in 1983. Informed written consent was obtained from each participant.

Men or women aged between 18 and 60 y were invited to enter the study if their body weight was ≤155 kg (the upper weight limit of the radiologic equipment), if their weight was stable (within ±5 kg) over the previous 3 mo, and if their BMI was ≥50 (women) or ≥40 (men). Sex-specific BMI criteria were set based on the advice of surgeons who report greater surgical difficulty in men than in women between a BMI of 40 and 50. Patients were excluded if they displayed any medical contraindications to the use of a VLED, including severe hepatic disease, advancing renal disease, and unstable cardiac disease (21). Persons with a "high-risk" alcohol intake [based on the National Health and Medical Research Council Australian Alcohol Guidelines, defined as >7 standard drinks/d or >43 standard drinks/wk for men and >5 standard drinks/d or >29 standard drinks/wk for women (22)] were also excluded.

Very-low-energy diet

Subjects consumed a VLED (Optifast VLCD) during the 12-wk dietary intervention. Ingestion of 3 shakes/d provides 1906 kJ (456 kcal), 52 g protein, 7 g fat, and 45 g carbohydrate plus the recommended daily intake of vitamins, minerals, and trace elements. The inclusion of ≈250 g (up to 2 cups) of low-starch vegetables was encouraged, such that total energy intake was between 1906 and 2844 kJ/d (456–680 kcal/d). Patients were advised to drink ≥2 L water and other calorie-free beverages each day and be physically active where able. Requirements of the VLED were outlined by a dietitian before commencement of the diet, and all subjects attended fortnightly dietetic counseling thereafter. The VLED was ceased at the end of the 12th week, which in most cases corresponded with the day before surgery. Adherence to the diet was not used to assess suitability for LAGB surgery, and poor compliance was not a contraindication to surgery. There was no planned refeeding period.

Computed tomography measurements: liver, VAT, and SAT

To assess changes in liver volume, all subjects underwent an abdominal computed tomography (CT) scan (Asteion Multislice System; Toshiba America MRI Inc, San Francisco, CA) before commencement and at completion of the 12-wk VLED. All investigations were performed in a supine position during a single breath hold while the arms were extended overhead. On the basis of the procedures of Schiano et al (23), a scout view of the upper abdomen was obtained to plan the examination. Contiguous 8-mm slices were then taken, including at least one image superior to and one image inferior to the liver, to ensure that the entire organ was captured. The scan was performed by using a spiral sequence without contrast medium (kV = 120, mA = 250, gantry rotation = 0.75 revolution/s, table speed = 48 mm/s, effective pitch = 4.5, matrix = 512 × 512, and field of view = 500 mm). Changes in VAT and SAT area were determined through comparison of a single transaxial image at the level of the intervertebral space between the second and third lumbar vertebrae (L2–L3) (24, 25). These images were taken while the liver scan was performed at baseline and week 12.

All CT scans were assessed by using Asteion Multislice System software (Toshiba America MRI Inc). To measure actual liver volume, the planimetric technique was used. A line was carefully drawn around the border of the liver on each contiguous scan, and the cross-sectional area within was automatically calculated. To determine the total liver volume in cubic millimeters, the area of all slices was summed and multiplied by 0.8 cm (the slice thickness). One hundred thousand mm^3 = 1 L.

CT-derived VAT and SAT were measured according to the procedures of Rössner et al (26). A trace was drawn around the outer edge of the abdomen and total fat area determined by calculating the pixel distribution with attenuation values between −150 and −50 Hounsfield units. According to the recommendations of Shen et al (27), a trace was then drawn inside the muscle layer of the abdominal cavity, and VAT was determined by calculating the fat area encircled within. The SAT area was considered to be the adipose tissue outside the muscle layer of the abdominal cavity, derived by subtracting VAT area from the total abdominal fat measurement. Paired measurements of total and SAT area were not available for 14 subjects (44%) because of the extension of the abdomen outside the field of view.

All CT scans and assessments were carried out by 2 skilled radiographers. Reexamination of 30% of liver volume, VAT, and SAT measurements by both technicians showed no significant differences between the initial and repeated calculations either within or between observers. Spearman's correlation coefficients between both radiographers were high for liver volume ($r = 0.985$, $P < 0.001$), VAT ($r = 0.985$, $P < 0.001$), and SAT ($r = 0.991$, $P < 0.001$). The interobserver CV was 1.0%, 2.1%, and 1.8% for liver volume, VAT, and SAT, respectively. Mean volume and area calculations of both observers were compared with the initial measurements, to yield Spearman's correlation coefficients were $r = 0.992$ for liver volume ($P < 0.001$), $r = 0.982$ for VAT ($P < 0.001$), and $r = 0.987$ for SAT ($P < 0.001$). Intraobserver CVs based on a comparison of the initial measurements and remeasurements for each radiographer were 2.4% and 2.0% for liver volume, 2.0% and 1.7% for VAT, and 3.1% and 1.0% for SAT.

Magnetic resonance imaging measurements: liver and VAT

The pattern of liver size reduction during the 12-wk period was examined in a subgroup of 9 subjects with an initial CT-derived liver volume measurement >2.8L. Consecutive magnetic resonance imaging (MRI) of the liver and abdomen was conducted at weeks 2, 4, 8, and 12 of the diet. Whenever possible, the protocol

for CT- and MRI-derived measurements was equivalent. The procedures for MRI were also based on the procedures of Schiano et al (23) and in accordance with the methods of others who used MRI (28, 29). MRI was carried out by using the Signa Hi Speed Plus 1.5 Tesla (General Electric, Milwaukee, WI). As was done for CT, all investigations were performed while the subjects were in a supine position during suspended respiration with the arms raised overhead. After an initial scout view was made, contiguous 8-mm slices were taken from the superior to the inferior aspect of the liver. The images were obtained by using a contiguous axial T1-weighted gradient echo pulse sequence (repetition time = 285 ms, matrix = 256 × 160, field of view = 480 mm, flip angle = 90°).

MRI sections were stored to CD-ROM and transferred to a workstation containing a computer-based digitizing system (Image J; National Institute of Health, Bethesda, MD). With the use of the planimetric technique, a line was carefully drawn around the border of the liver on each contiguous scan, and the cross-sectional area within was automatically calculated by using the software. The area of all slices was summed and multiplied by 0.8 cm (the slice thickness) to determine total liver volume.

Single-slice transaxial images at the level of L2–L3 were used to assess changes in the VAT compartment by using the same protocol as for CT. These images were taken during the liver scan at weeks 2, 4, 8, and 12. Because of the extension of the abdomen outside the field of view, an accurate series of SAT measurements was obtained in 3 of the 9 subjects (33%) who completed the MRI scans. Because of this small sample size, the pattern of SAT change relative to liver volume, weight, and VAT was not examined.

To assess the VAT area, the abdominal slice at L2–L3 was identified within the sections stored to CD-ROM and transferred to a workstation containing SliceOmatic (version 2.4, Rev-1; TomoVision, Montreal, Canada). Because of the strong signal intensity produced by adipose tissue when visualized by MRI, fat is easily differentiated from surrounding tissue. The SliceOmatic software compares the intensity of each pixel within an image with that of adjacent pixels and automatically generates a border to separate sections of the image that significantly differ in signal strength. This creates a "jigsaw" effect, which enables easy identification of sections of tissue with similar pixel intensity; a mouse-click inside each piece of the VAT jigsaw colors that section of the image. As for the CT protocol, the inner margin of the abdominal cavity demarcated the outer border of the VAT compartment. Each scan was then manually edited within the program to ensure that light sections of the bowel were excluded and the boundaries were clearly defined. The software determined the area of colored VAT, providing a measurement in square centimeters.

All MRI sections were calculated by a single operator. Reexamination of 30% of liver volume and VAT measurements showed no significant difference between the initial and repeated calculations. Spearman's correlation coefficients were high for liver volume ($r = 0.998$, $P < 0.001$) and for VAT ($r = 0.993$, $P < 0.001$). The intra-observer CV was 0.7% for liver volume and 2.4% for VAT.

To assess the level of agreement between CT- and MRI-derived liver volume and VAT calculations, 11 paired measurements (2 at baseline and 9 at week 12) were available. For the assessment of liver volume, the correlation between the 2 methods was high ($r = 0.989$, $P < 0.001$). Analysis according to the recommendations of Bland and Altman (30, 31) showed a trivial mean bias of 0.0024 L toward MRI (limits of agreement of ±0.1736). For the measurement of VAT, the correlation between the 2 methods remained high ($r = 0.866$, $P = 0.001$). Bland and Altman analysis showed a mean bias of 14.85 cm^2 toward MRI (limits of agreement ±51.2), which indicates that, although the agreement between the 2 methods was very good, MRI-derived VAT measurements tended slightly higher. Neither liver volume nor VAT measurements showed any change in bias across the range of measurements.

Anthropometric measurements

Weight was recorded with the use of the electronic Tanita Wedderburn TBF-305 (Lake Worth, FL) while the subjects were wearing light clothing and no shoes. Height was determined with a wall-mounted stadiometer. Neck circumference was taken immediately above the thyroid cartilage, waist circumference at the narrowest point between the lower rib margin and the iliac crest, and hip circumference at the widest point over the greater trochanters. Seated blood pressure was recorded. All measurements were taken at baseline and then fortnightly throughout the study period by a single clinician.

Laboratory tests

Baseline and 12-wk metabolic variables were assessed by a series of biochemical and hematologic tests. The analysis consisted of liver function tests, the measurement of fasting glucose metabolism (which included plasma glucose, plasma insulin, and glycated hemoglobin A_{1c}), the determination of a fasting lipid profile (which included measurements of total cholesterol, LDL cholesterol, HDL cholesterol, and triacylglycerol), and the measurement of C-reactive protein (CRP). The analyses were performed in an approved laboratory with internal and external quality control by standard laboratory assays.

Assessment of dietary compliance and acceptability

Dietary compliance was assessed by using urinary ketone reagent strips (Keto-Diastix; Bayer Diagnostics Manufacturing Ltd, Bridgend, United Kingdom) to assist ongoing monitoring and counseling and not for the purpose of predicting or testing postsurgical dietary adherence. After the first week of a VLED, an increase in the urinary excretion of ketoacids occurs subsequent to increased fat catabolism (32); therefore, the presence of at least traces of ketones in the urine was considered to indicate net lipolysis and dietary adherence. Urine samples were collected on the day of each biweekly consultation. The absence of ketones scored 0, a trace amount of ketones scored 1, a small amount scored 2, and a moderate amount scored 3 points. For the purpose of analysis, the last observation carried forward was used for a single missing value in 6 patients (<1% of total measurements). Ketone scores determined at visits every 2 wk were summed for each patient.

Qualitative methods were used to measure product side effects and acceptability. During the counseling sessions, the subjects were asked to rate 6 factors on a 5-point Likert scale: product taste (1, highly unacceptable; 2, unacceptable; 3, tolerable; 4, acceptable; 5, highly acceptable), hunger (1, extreme hunger; 2, hungry most days; 3, hungry some of the time; 4, occasional hunger; 5, no hunger), nausea or vomiting (1, daily; 2. 4–6 times/wk; 3, 2–3 times/wk; 4, ≤1 time/wk; 5, none), bowel function (1, constipation defined as no bowel movement in the past 4 d; 2, constipation defined as no bowel movement in the past

TABLE 1
Descriptive characteristics of subjects before and after a 12-wk very-low-energy diet[1]

Characteristic	Baseline	After 12 wk	Mean change[2]
			%
Body weight (kg)	139.8 ± 11.0[3]	125.0 ± 11.7	−10.6 (−0.7 to −19.1)
BMI (kg/m^2)	47.3 ± 5.3	42.3 ± 5.5	−10.6 (−0.7 to −19.1)
Waist circumference (cm)	140.8 ± 9.8	128.1 ± 10.0	−9.0 (0 to −19.2)
Neck circumference (cm)	45.9 ± 3.8	43.2 ± 3.2	−5.9 (2.1 to −15.3)
Systolic BP (mm Hg)	154.3 ± 18.3	136.0 ± 18.1	−11.08 (13 to −37)
Diastolic BP (mm Hg)	90.7 ± 9.8	80.9 ± 11.2	−10.24 (22 to −34)
Liver volume (L)	2.8 ± 0.5	2.3 ± 0.4	−18.7 (20 to −51.6)
L2–3 VAT area (cm^2)	346.3 ± 103.3	285.1 ± 89.3	−16.9 (11.8 to −52.6)
L2–3 SAT area (cm^2)[4]	454.5 ± 114.8	375.7 ± 109.7	−17.7 (2.9 to −40)

[1] $n = 32$ paired results. A significant liver volume reduction of 0.5 L (1 SD) was achieved by 15 subjects (47%). Eleven of the 15 subjects had a baseline liver volume > 2.8 g/L at baseline. Six of the 15 subjects achieved a reduction of 1.0 L (2 SD), all of whom had a baseline liver volume > 2.8 L. BP, blood pressure; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.
[2] All values are $\bar{x}$; range in parentheses. All changes are statistically significant, $P < 0.001$ (paired-samples t test).
[3] $\bar{x}$ ± SD (all such values).
[4] $n = 18$.

2–3 d; 3, normal; 4, increased frequency; 5, diarrhea), emotional eating (1, daily; 2. 4–6 times/wk; 3, 2–3 times/wk; 4, ≤1 time/wk; 5, none), and social eating (1, daily; 2. 4–6 times/wk; 3, 2–3 times/wk; 4, ≤1 time/wk; 5, none). Emotional eating was defined as "eating foods outside the diet's guidelines, due to emotional reasons such as stress, sadness, anger or frustration." Social eating was defined as "eating foods outside the diet's guidelines, because you are in a social setting." Median group ratings for each factor at weeks 4 and 10 were compared. A person's aggregate score of each factor over all 12 wk was also assessed against their total percentage weight loss.

Data analysis

Effects of the 12-wk VLED program were directly compared by using the paired-samples t test for continuous variables. The pattern of liver volume, abdominal fat, and body weight change over the 12-wk VLED was expressed as a percentage and plotted over time. The difference in mean liver volume, VAT, and weight measurements at baseline and 2, 4, 8, and 12 wk was assessed by analysis of variance with the use of Tukey's post hoc analysis and paired-samples t test for normally distributed data. Simple bivariate analysis assessed for correlations between initial liver volume and all baseline characteristics, the percentage change in liver volume and all other measures, the average ketone score, total acceptability scores, and cumulative weight loss. Forward and backward linear regression identified factors independently predictive of a larger liver volume and liver volume change over the 12-wk period. Two quantitative laboratory variables—fasting plasma insulin and γ-glutamyltransferase—required log transformation before parametric analysis. SPSS version 12.0.1 was used for the statistical analysis. A P value <0.05 was considered statistically significant.

RESULTS

Thirty-seven subjects were recruited into the study and commenced the 12-wk VLED protocol; however, 5 subjects (14%) failed to establish a pattern of dietary compliance during the first 2 wk. Four of these subjects (80%) reported ongoing taste intolerance resulting in nausea and occasionally vomiting as the main reason for noncompliance, whereas the other subject failed to comply primarily because of major instability in his personal life. These 5 subjects, which included 2 members of the subgroup of 12 undergoing a series of MRIs, were excluded from further investigation. All subjects continuing past week 2 were considered part of the study. There were no other patients who revoked consent or were lost to follow-up, but one subject in the MRI subgroup chose to discontinue the additional measurements because of feelings of claustrophobia inside the MRI apparatus but remained in the study. In total, 32 subjects (86%) completed the 12-wk protocol, and 9 of these subjects (75% of the initial MRI subgroup and 28% of the final study group) underwent the additional MRI scans at weeks 2, 4, 8, and 12.

The subject group consisted of 19 men and 13 women, and their mean (±SD) age was 47.9 ± 9.1 y. Descriptive characteristics of the 32 bariatric surgery candidates are presented in **Table 1**. Body weight ranged from 116 to 155 kg and the BMI categories ranged from morbidly obese to super obese (40.4–61.9). CT assessment showed a mean liver volume of 2.8 L (range: 2.0–3.9 L), a mean VAT deposition of 346.3 cm^2 (range: 163.9–556.0 cm^2), and a mean SAT measurement ($n = 18$) of 454.53 cm^2 (range: 252.5–699.3 cm^2). Thirteen of the 32 subjects had type 2 diabetes (41%), 16 were taking a lipid-lowering medication (50%), 24 were taking an antihypertensive agent or recorded a baseline blood pressure >140(systolic)/90 (diastolic) mm Hg (75%), and 14 had ≥1 abnormal result from the liver function test (44%). Baseline biochemical variables are shown in **Table 2**.

At completion of the 12-wk VLED, all baseline descriptive characteristics for the 32 subjects decreased significantly: body weight by 14.8 ± 7.2 kg, BMI by 5.0 ± 2.4, liver volume by 0.56 ± 0.50 L, VAT by 61.2 ± 52.1 cm^2, and SAT by 78.7 ± 50.1 cm^2 (Table 1). Neither age nor sex predicted the extent of the tissue reduction. An example of a cross-sectional CT-derived image of the liver at baseline and week 12 is shown in **Figure 1**. Overall, there was no difference in the relative reduction of liver volume, VAT, or SAT (18.7%, 16.9%, and 17.7%, respectively). Repetition of this comparative analysis in the subgroup of 18 subjects with paired SAT measurements yielded a similar reduction of 19.2% in liver volume, of 17.6% in VAT, and of 17.7% in SAT.

Except for a higher initial liver volume, the baseline demographic and clinical measurements of the 9 subjects who took part in the series of MRI scans did not differ significantly from

TABLE 2
Changes in measures of glucose metabolism, lipids, liver function, and a marker of inflammation before and after a 12-wk very-low-energy diet[1]

Characteristic	Baseline	After 12 wk	P^2
ALP (U/L)	93.2 ± 31.4 (59–211)[3]	84.5 ± 24.2 (52–159)	0.001
AST (U/L)	27.4 ± 12.7 (14–73)	24.8 ± 11.3 (11–59)	NS
ALT (U/L)	40.6 ± 23.6 (11–121)	32.8 ± 18.1 (9–105)	0.05
GGT (U/L)[4]	38.0 ± 39.0 (16–259)	30.0 ± 21.0 (10–227)	<0.001
Bilirubin (umol/L)	11.1 ± 6.5 (4–30)	13.0 ± 8.3 (6–45)	0.011
Fasting glucose (mmol/L)	7.6 ± 3.4 (4.5–17.2)	6.1 ± 11.7 (3.8–16.4)	0.011
Fasting insulin (mIU/L)[4,5]	24.0 ± 15.0 (11–164)	17.0 ± 13.0 (7–85)	<0.001
Glycated hemoglobin A_{1c} (%)	7.2 ± 1.8 (5.6–12.7)	6.3 ± 1.1 (5–9.6)	<0.001
Cholesterol (mmol/L)	5.0 ± 0.95 (3–6.8)	4.5 ± 1.2 (2.4–6.5)	<0.001
Triacylglycerol (mmol/L)[5]	1.8 ± 0.68 (0.8–3.1)	1.5 ± 0.69 (1–3)	0.043
HDL cholesterol (mmol/L)	1.3 ± 0.29 (0.8–2.3)	1.3 ± 0.25 (0.8–2.0)	NS
LDL cholesterol (mmol/L)	2.9 ± 0.87 (1.1–4.7)	2.5 ± 1.0 (0.8–4.5)	0.001
CRP (mg/L)	11.4 ± 9.6 (3–39.1)	10.8 ± 10.0 (1–43.6)	NS

[1] $n = 31$ paired results. ALP, alanine phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ glutamyltransferase; CRP, C-reactive protein.
[2] Paired-samples *t* test.
[3] $\bar{x}$ ± SD; range in parentheses (all such values).
[4] Denotes log-transformed data for nonnormal distribution. Data presented are median ± interquartile range (range).
[5] Denotes data for which one outlying variable has been removed and excluded from all subsequent calculations.

those of the main study group. A significantly greater baseline liver volume of 3.4 ± 0.42 L compared with 2.6 ± 0.45 L ($P < 0.001$) reflects the fact that only subjects with an initial liver volume measurement ≥2.8L were invited into the MRI subgroup. The relative changes in body weight, liver volume, and VAT are shown in **Figure 2**. The total decrease in liver size was 28.7%. An immediate decrease in liver volume took place; 80% of the observed size reduction occurred between weeks 0 and 2 ($P < 0.001$). The pattern of VAT and weight reduction showed a more progressive decrease. The mean VAT decreased by 24.1% between weeks 0 and 12 ($P = 0.001$). The mean total weight loss in the group of 9 was 11.1% between weeks 0 and 12 ($P < 0.001$).

Focusing on the change in liver volume in the 32 subjects with paired baseline and 12-wk measurements, the total percentage reduction in liver volume was strongly predicted by both the relative reduction in body weight ($r = 0.54$, $P = 0.001$) and the initial liver volume ($r = 0.43$, $P = 0.015$). Together these variables contributed 45% of the variability in the relative change in liver volume ($P < 0.001$). Subjects with a greater baseline liver volume lost proportionately more liver size over the course of the 12-wk VLED, as illustrated in **Figure 3**. Categorization of the group into initial liver volume ≤2.99 L ($n = 20$) or ≥3.0 L ($n = 12$) showed a significantly greater mean size reduction in the group with larger livers (26.9% compared with 13.8%; $P = 0.011$). There was no correlation between the initial VAT and SAT measurements and the relative change in VAT and SAT area, respectively.

The demographic characteristics of the 5 subjects who failed to establish a pattern of dietary compliance during the first 2 wk of the study were not significantly different from the study group; therefore, their anthropometric, biochemical, and radiologic data were included in the assessment of factors associated with initial liver volume. When the baseline liver volume measures for the 37 subjects were corrected for age, sex, and BMI, linear regression yielded 3 factors with significant independent predictive effects on baseline liver volume: triacylglycerol (33%; $\beta = 0.528$, $P \leq 0.001$), diastolic blood pressure (10%; $\beta = 0.310$, $P = 0.021$),

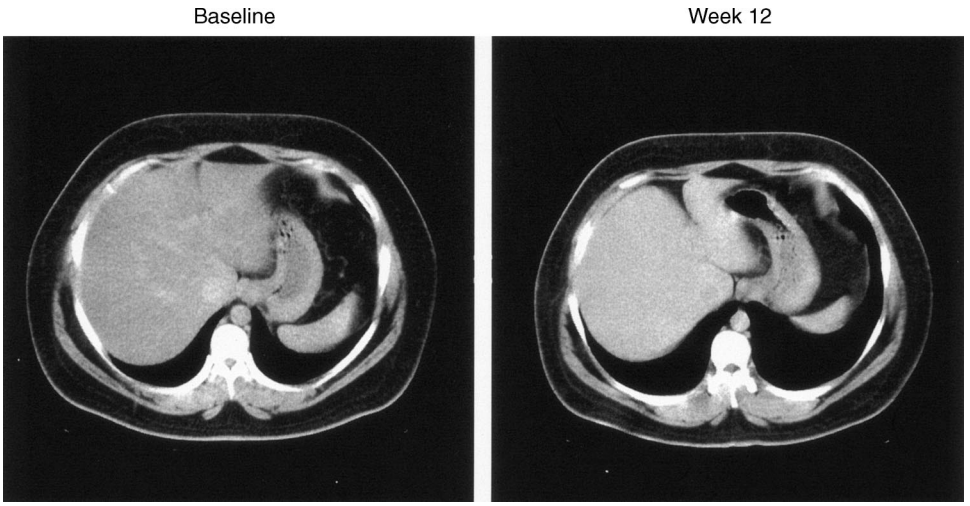

FIGURE 1. Single cross-sectional images of the liver performed by computed tomography at baseline and week 12 of a very-low-energy diet. The images, taken from within a series of contiguous 8-mm slices used to calculate total liver volume, illustrate the extent of the change in liver volume with weight loss in a 35-y-old man with an initial liver volume of 3.7 L and a final liver volume of 2.4 L. A 35% reduction in liver size and a weight loss of 18 kg were observed.

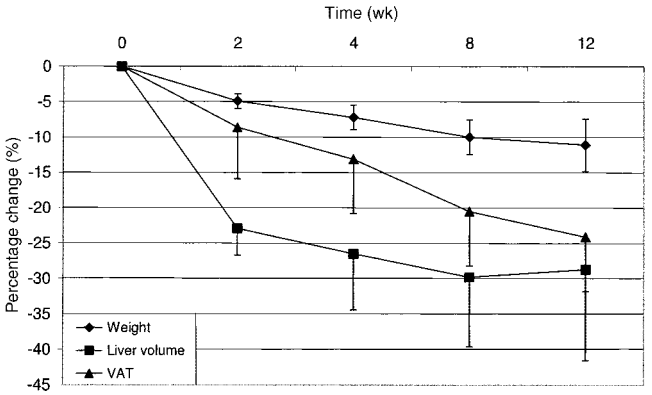

FIGURE 2. Relative change in liver volume, visceral adipose tissue (VAT) area, and body weight during a 12-wk very-low-energy diet as measured by serial magnetic resonance imaging ($n = 9$). An immediate reduction in liver volume occurred in the first 2 wk ($P < 0.001$) and between baseline and all other time points ($P < 0.001$ for all). The decreases in body weight and VAT showed a more uniform change. Significant decreases in weight ($P < 0.001$) and VAT ($P = 0.001$) occurred between baseline and week 12. The statistical analysis was conducted by using ANOVA; Tukey's post hoc analysis was used for normally distributed data and paired-samples *t* test.

and CRP (8%; $\beta = 0.297$, $P = 0.025$). Together these factors contributed 51% of the variability in initial liver volume ($P < 0.001$). The change in triacylglycerol over the 12-wk VLED showed a weak relation to the change in liver volume but was not significant ($r = 0.33$, $P = 0.08$).

Urinary ketone analysis was performed 6 times throughout the duration of the diet in 26 subjects and 5 times in the remaining 6 subjects. The total ketone score was highly correlated with the total percentage weight reduction at completion of the diet ($r = 0.66$, $P < 0.001$).

Ratings of taste acceptability in the 32 subjects averaged "acceptable" during the first 8 wk of the diet; nevertheless, taste acceptability deteriorated over time: median scores decreased significantly from week 4 to week 10 ($P < 0.001$). When the summed taste rating for each subject was compared with their total percentage weight loss, a strong positive correlation emerged ($r = -0.57$, $P < 0.001$). There were no reports of nausea or vomiting throughout the duration of the diet. At wk 4 hunger ratings averaged 'occasional hunger', however median hunger scores were significantly higher at wk 10 ($P < 0.001$). Median total hunger ratings were also inversely related to total relative weight loss ($r = -0.66$, $P < 0.001$). Similar to hunger, scores for emotional eating ($P < 0.001$) and social eating ($P < 0.001$) increased significantly between wk 4 and wk 10. Emotional eating was positively correlated with hunger score ($r = 0.72$, $P < 0.001$) and negatively correlated with total percentage weight loss ($r = -0.80$, $P < 0.001$). Social eating was not related with any other factor.

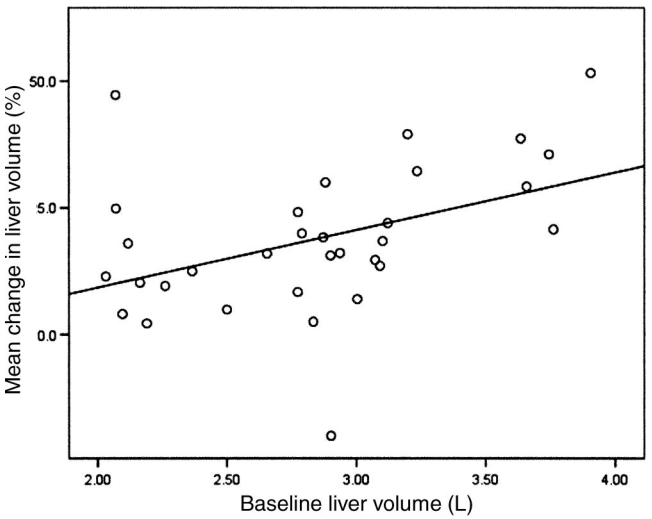

FIGURE 3. Comparison of the mean reduction in liver volume between subjects according to initial liver size ($n = 32$). Subjects with larger livers experienced a significantly greater decrease in liver volume than did those with a smaller baseline liver volume ($r = 0.43$, $P = 0.015$; simple bivariate statistical analysis).

Most biochemical measures showed improvement by the completion of the study, and no deterioration in any clinical condition was observed (Table 2). Constipation was the most common side effect. Seven subjects (21.9%) reported "no bowel movement in the past 4 d" at some stage during the diet, and another 10 subjects reported "no bowel movement in the past 2–3 d." Constipation was usually moderated by increased fluid and vegetable intakes, the addition of a fiber supplement, or the addition of a mild laxative. Other reported side effects included light headedness (16%), cold intolerance (6%), and dry skin (3%).

Finally, none of the subjects enrolled in the study had hepatomegaly at the time of surgery. There were no conversions to an open procedure, no major perioperative complications, and no prolonged hospital stays. This study, however, was not adequately powered to measure a change in perioperative complication rates, and the study design did not include a control group.

DISCUSSION

In a severely obese population, we investigated a range of factors related to aspects of efficacy and acceptability of preoperative weight loss with the VLED. Importantly, examination of the pattern of change in liver volume showed that most of the volume reduction occurred in the first 2 wk of weight loss, whereas VAT and body weight decreased at a uniform rate over the 12-wk study period. At the conclusion of the diet, the average decrease in liver size was 18.7%. The change in liver volume was linearly related to initial liver volume (13.8% in livers <3.0 L and 26.9% in livers ≥3.0 L) and the relative reduction in body weight. Thus, for a given weight loss, those with larger livers can be expected to undergo a preferential reduction in liver size, the preponderance of which occurs in the first 2 wk but which continues to occur to a maximum effect at 8 wk. Favorable, and largely predictable changes with weight loss, were also observed for a range of biochemical, clinical, and anthropometric measures.

We found only 2 previous studies that examined changes in liver volume during weight loss. Fris (33) used ultrasound to assess changes in the size of the left lobe of the liver and used bioelectrical impedance to assess total body fat in 40 obese subjects (median BMI: 47 ± 6.8) after a 2-wk VLED. Notwithstanding methodologic differences, significant liver volume reductions were recorded, which correlated with the decrease in BMI but not with estimated fat mass.

Busetto et al (34) assessed liver size and body fat distribution via whole-body multislice MRI in 6 premenopausal women losing weight after LAGB. This small sample had a mean baseline

BMI of 42.6 ± 1.1 and a mean liver volume of 1.79 ± 0.41 L. Weight loss, liver volume, and body fat reduction were reassessed at 8 wk and 24 wk post-LAGB. Significant decreases in body weight and the total fat measurement occurred at both time points, whereas reductions in liver size and VAT occurred only in the first 8 wk. Liver volume and VAT were significantly correlated at baseline, but no association was found between liver size and total or regional fat measurements during weight loss. We found no association between liver volume and VAT at any time point. The mechanism explaining this relative reduction relates to the disposition of fat. In mild liver steatosis, abnormal accumulation of lipid is predominately in centrilobular hepatocytes, whereas, with increasing steatosis, more and more hepatocytes throughout a greater area of the liver lobule accumulate lipid (35). In severe steatosis, a greater proportion of cells can reduce their size when abnormal lipid accumulations are dissipated during weight loss. This contrasts with changes in adipose tissue; adipocytes have a more uniform reduction in size with weight loss.

To our knowledge, this is the first study to measure and compare changes in liver volume, VAT, and SAT and the first study to investigate their pattern of change over the first 12 wk of weight loss. CT was selected for most of the measurements because of its proven accuracy for assessing liver volume (23, 36) and VAT (26, 37, 38), more moderate expense, and shorter acquisition time, which reduces movement artifacts and affords high accuracy and precision (27). However, the utility of CT for serial measurements is limited because of the emission of ionizing radiation. For this reason, MRI was chosen for the sequential scans to assess ongoing change. Similar to CT, MRI determination of liver volume (29, 39) and VAT (40–42) has shown high accuracy and clinical utility. CT and MRI previously showed similar variances in planimetry liver volume calculations (43) and estimation of visceral fat areas (37). Our own volume and area calculations supported the close agreement of these 2 methods.

Despite the limited power of this study, we found that triacylglycerol showed a strong independent association with baseline liver size. The association between an elevated triacylglycerol concentration and liver size has not been examined, but an elevated triacylglycerol concentration is commonly associated with liver steatosis and liver disease; high rates of between 20% and 80% have been shown in patients with NAFLD (44). In an earlier study we found a significant correlation between fasting triacylglycerol concentrations and liver steatosis (2). An elevated CRP concentration, a marker of nonspecific inflammation, and an elevated diastolic blood pressure were also positive predictors of liver volume. All 3 factors, which contributed 51% of the variability in baseline liver size, are considered to be components of the expanded metabolic syndrome (45), of which NAFLD is now also deemed a part (2, 46).

To facilitate dietary adherence and success, the subjects underwent fortnightly supervision and counseling from an experienced dietitian. The close correlation between total weight reduction and urinary ketones measured during these meetings supports the use of this simple, noninvasive method to monitor ongoing dietary compliance. Initially, hunger and emotional eating were well controlled in most subjects; however, in the latter stages these factors increased and taste acceptability decreased. Reports of hunger and food cravings during a VLED appear to be less than reports during conventional low-calorie diets (47). Nonetheless, the increase over time was most likely related to boredom and fatigue with the ongoing dietary restriction.

A recommended time period for the use of a VLED before surgery is a judgement based on a balance between the possible benefits of small additional weight loss and boredom, fatigue, and poor compliance. Given the early significant reduction in liver volume and the slower more consistent reduction in weight and VAT, we suggest that the minimum time for a preoperative VLED be 2 wk. Extending this dietary intervention to 6 wk will achieve an optimal balance between maximal reduction of liver size, and useful reductions in VAT stores and body weight, without compromising patient compliance and acceptability.

One limitation of this study was the relatively small selected sample of morbidly obese persons seeking bariatric surgery. Secondly, different methods were used to determine the pattern of liver volume and VAT reduction; however, both techniques are highly reliable and showed a very close correlation. Finally, a liver biopsy, which is required for definitive diagnosis of fatty liver, was not performed at patient entry into the study because it would have been unethical to undertake this procedure when not clinically indicated. We previously showed that liver size independently predicts the level of hepatic steatosis at laparoscopy (2); therefore, the hepatomegaly identified in this study was considered to reflect a high level of fatty infiltration into the liver. In the early stages of VLED, the low-carbohydrate content of the diet will also result in depletion of liver glycogen stores. The level of glycogen reserve is highly dependent on recent dietary intake (48), averaging ≈400 g healthy persons (48, 49). Each gram of stored glycogen binds 3–4 g water (50); therefore, diminution of liver glycogen may contribute up to 40% of the observed volume reduction.

In summary, severely obese persons who are compliant with a 12-wk VLED can safely and effectively achieve significant reductions in body weight, liver volume, VAT, and SAT before laparoscopic surgery—improvements that are likely to diminish the degree of surgical difficulty and decrease the risk of liver trauma and blood loss. Of particular note is the fact that most of the reduction in liver size occurs in the first 2 wk of weight loss with a VLED, whereas the reduction in VAT and weight is more uniform over a 12-wk period. Several components of the metabolic syndrome may predict the presence of an enlarged liver, but those with massive hepatomegaly will experience a liver volume loss of greater magnitude without special attention. The VLED was an acceptable means of preoperative weight loss in most of the subjects, and, apart from mild transitory side effects, no unfavorable anthropometric, biochemical, or clinical outcomes were found.

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SLC was responsible for designing the experiment, writing the study protocol, collecting and analyzing the data, and writing the manuscript. JBD was responsible for designing the experiment, overseeing the writing of the study protocol, collecting and analyzing the data, and writing the manuscript. PM was involved in designing the experiment, in overseeing all radiologic measurements, and with writing the manuscript. BJS assisted with the MRI analysis and with writing the manuscript. PEO was responsible for designing the experiment, overseeing the writing of the study protocol, collecting the data, and writing the manuscript. None of the authors had a conflict of interest.

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