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EFFECTS OF TWO PREOPERATORY WEIGHT LOSS DIETS ON HEPATIC VOLUME, METABOLIC PARAMETERS, AND SURGICAL COMPLICATIONS IN MORBID OBESE BARIATRIC SURGERY CANDIDATES: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Objective: To assess which type of preoperative dietary strategy is most effective in reducing liver volume and assessing its influence on different biochemical parameters and on surgical complications in individuals undergoing bariatric surgery.

Methods: Parallel randomized trial comparing the effect of a very low calorie diet (VLCD) and a low calorie diet (LCD) for a period of 21-days before surgery on hepatic volume, anthropometric and biochemical parameters. Compliance and tolerance to the diets, surgical complications and hospital stay were also determined.

Results: Eighty-six morbid obese participants undergoing bariatric surgery were randomized. The hepatic volume was significantly reduced in both intervention groups, but no differences in changes between groups were detected. The reduction in the hepatic volume was higher in those patients with a baseline hepatic volume >3L compared to those with <3L (adjusted P-value <0.001). The percentages of total weight lost were 5.8% and 4.2%, (adjusted P-value=0.004) for participants on the VLCD and LCD, respectively. There were no differences between groups for any of the biochemical parameters analyzed, nor in the number of surgical complications nor the length of hospital stay. Adherence to the diet was good; nevertheless, participants in the VLCD intervention showed worse tolerance.

Conclusions: In subjects with morbid obesity undergoing bariatric surgery, compared to a LCD, a preoperative 21-day intervention with VLCD is more effective in terms of reducing total body weight but not in terms of reducing the liver volume. Both types of preoperative diets have similar effects on clinical biochemical parameters, rate of surgical complications, and hospital length stay.

Key words: preoperative diet; bariatric surgery; liver size; weight loss.

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INTRODUCTION

Obesity is a pandemic disease that affects 10.8% of men and 14.9% of women worldwide aged 18 or older, according to the latest data presented by the WHO [1]. Among these, 55 million people suffer from morbid obesity, which is frequently associated with comorbidities such as type 2 diabetes mellitus (T2DM), hypertension (HT), dyslipidemia (DLP), obstructive Sleep Apnea Syndrome (OSAS) and non-alcoholic fatty liver (NAFLD).

NAFLD is prevalent in subjects with obesity, insulin resistance or T2DM and dyslipidemia [2]. The prevalence of NAFLD or hepatomegaly among severely obese patients undergoing bariatric surgery exceeds 90%, of which approximately 5% of these patients may have unsuspected cirrhosis [3].

The most effective method for reversing morbid obesity and improving the comorbidities is bariatric surgery [4]. However, morbidly obese patients present a high surgical risk due to the thickness of the abdominal wall, which can limit the accuracy of the surgical procedure; excess intra-abdominal fat, which hinders the technical procedure; and thickening of the liver, which impairs the vision of the gastroesophageal area and makes it more friable and thus more susceptible to bleeding.

Some studies suggest that the prescription of a very low calorie diet (VLCD) before bariatric surgery may be useful in order to control diabetes and other comorbidities associated with obesity [3,4], and especially useful for decreasing liver volume in those patients with hepatic steatosis [5,6]. Moreover, this preoperative dietary strategy has been suggested to reduce the risk of surgery [7]. However, despite the published studies, randomized studies at this level have not yet evaluated weight loss and its influence on biochemical parameters, hepatic volume, and the risk of surgery complications. This has led the American Society for Metabolic

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and Bariatric Surgery (ASMBS) to state that there is not enough scientific evidence to recommend a specific pre-operative diet [8].

The present work used a parallel randomized controlled clinical trial to compare the effect of two dietary interventions (very low calorie diet versus low calorie diet) on liver volume, anthropometry, biochemical parameters, compliance and tolerance of dietary intervention as well as complications of bariatric and hospital stay.

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MATERIALS AND METHODS

Trial design

The present study is a parallel randomized trial with a balanced randomization [1:1] carried out at the Hospital of Sant Joan de Reus, Spain.

Participants

The study population consisted of men and women who were morbid obese candidates for laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) bariatric surgery. The inclusion criteria were as follows: men and women between 18 and 66 years old, with: a) a BMI≥35 kg/m^2 and associated comorbidities such as type 2 diabetes mellitus, hypertension, dyslipidemia, sleep apnea and obstructive sleep apnea-hypopnea syndrome; or b) a BMI≥40 kg/m^2 and whose conservative treatment had failed. The exclusion criteria were as follows: a) a BMI<35; b) pregnant or breast feeding women; c) severe systemic or organ pathology; d) insulin-treated; e) have coagulation problems; and f) have unresolved eating disorders or severe psychiatric pathology. The study was carried out in Hospital of Sant Joan de Reus, Spain. All the patients provided written informed consent for their participation, and the study was approved by the Ethical Committee of the Hospital Universitari de Sant Joan de Reus. All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments. The study was registered at ISRCTN (http://www.isrctn.com/ISRCTN16967604).

Intervention

Subjects were randomized to follow a VLCD or a low-calorie diet (LCD) for a period of 21 days. Both dietary interventions had the same percentage of macronutrients (46.8% carbohydrates, 36.4% protein, 9.3% fat, and 7.4% fiber) but differ in the energy content. The

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total amount of energy administered with the VLCD (4 sachets of Optifast®; Nestlé Health Science; 2011) was 800 kcal/day, and broth and non-calorie beverages were permitted. The LCD (1200 kcal/day) consisted of a mixed diet including two Optifast® sachets administered in the middle of the morning and in the afternoon. Thus, 800 kcal of the total daily intake came from food, while the other 400 kcal from the total of the Optifast® sachets provided. Twenty one different daily menus were provided to the participant to facilitate the adherence to the dietary intervention. Dietary counseling and monitoring was conducted by trained dietitians once a week during the 3 weeks of dietary intervention. During the study, the participants were advised to maintain the same level of physical activity.

Surgery procedures

All patients were operated by the same surgical team, under general anesthesia and with the patient in the Lloyd-Davis position. A five-port technique is used in all patients.

Laparoscopic Roux-en-Y Gastric Bypass (McLean-Gagner): Creation of the reservoir of 25 to 30 ml capacity verticalized up to the angle of His. The section of the jejunum is performed at 100 cm from the Treitz angle, and alimentary limb is positioned in antecolic and antegastric position. The gastrojejunal anastomosis is performed using 25 mm circular stapler that is inserted into the abdominal cavity through an enterotomy along the antimesenteric border. The enteric anastomosis is performed using a mechanical stapler and closing the resulting enterostomy with a continuous suture performed manually. Finally, Petersen space is closed in order to avoid internal hernias; gastrojejunal anastomosis is checked by air insufflation.

Laparoscopic Sleeve Gastrectomy: The dissection begins in the greater curvature of the stomach, guided by Faucher tube with a diameter of 38 Fr, separating it from the gastroepiploic arcade of the greater omentum. The section is performed at 3 cm of pylorus and continues

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vertically until the angle of His, releasing the posterior fundus to avoid leaving a residual pocket. To strengthen the suture line, we also used a polycarbonate polyglycolic absorbable reinforcement (Seamguard, WL Gore & Associates, Flagstaff, AZ, USA) that reduces the incidence of intra- and extraluminal bleedind. A methylene blue leak test is performed on all patients before the end of the surgery.

Outcomes

The main objective was to assess the effect of two dietary strategies (VLCD vs LCD) on liver volume in patients with morbid obesity pending bariatric surgery. As secondary endpoints, we also analyzed the effect of the two interventions on total body weight and composition, blood pressure, several biochemical parameters, compliance and tolerance with the dietary intervention, surgery complications and hospital stay.

Measurements

Hepatic volume, anthropometrics, biochemical parameters and compliance and tolerance with the intervention were determined before and after each dietary intervention (at 21 days). Surgical complications were recorded during the following 6 months after intervention.

Weight was registered at baseline visit, at the end of the dietary intervention (at 21 days) and at 6 months after surgical intervention.

At baseline we used the International Physical Activity Questionnaire (IPAQ) to assess the minutes of activity and sedentary lifestyle of the subjects.

Liver volume measured by computed tomography. Computed tomography (CT) scans (General electric discovery 750 HD; GE Medical System LLC, Waukesha, 2014. USA) were performed without intravenous or oral contrast. The liver volume was determined from the images taken between the lung bases and L3. The mean liver density was calculated in each

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subject with the Synapse 3D software at the beginning and end of the intervention. The results were expressed in liters.

Anthropometric and blood pressure measurements. Height was determined at the first visit using a wall stadiometer (Seca 223; 2010). Body weight and waist circumference were measured twice with the patient in fasting conditions, with light clothing and no shoes. The waist circumference was measured midway between the lowest rib and the iliac crest using an anthropometric tape. Total weight loss was determined from baseline to 21 days, from surgical intervention to 6 months and from baseline to 6 months after surgical intervention. Body composition and total water content were estimated by bioelectrical impedance (TANITA TBF-420; 2014). Blood pressure was taken twice per session after the patient had been at rest for at least 5 minutes using an automatic sphygmomanometer (Omron HEM-7121-E). The mean of these two measurements was used for the study.

Laboratory tests. The parameters analyzed at baseline and the end of the intervention were: Leukocyte and each subtype neutrophil, lymphocyte and monocyte counts; total serum protein, albumin, prealbumin; C-Reactive protein (CRP mg/dL); concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl-transferase (GGT); plasma creatinine, urea, estimated glomerular filtration rate (eGFR); serum glucose and insulin, and glycosylated hemoglobin (HbA_1c, %); lipid profile and serum uric acid concentrations.

Compliance and tolerance. The degree of compliance with the intervention was indirectly determined by: a) Recording the number of empty Optifast® (Nestle Health Science, Swizerland) sachets returned by the participants. The percentage of envelopes consumed was assessed in relation to the theoretical number of sachets consumed. A weekly record of the

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returned sachets was made and then the average of the three weeks was performed for the assessment of the compliance with the intervention. Participants were classified as high adherent or low-adherent when the consumption of the envelopes was ≥ 80% or < 80%, respectively; and, b) Recording the non-allowed foods consumed during the intervention. The extra food items not allowed in the diet were registered weekly and averaged: Participants compliance was classified as: very good (no extra food during the intervention period), good (one or two extra food), fair (three extra food) or bad (four or more extra food).

Dietary intervention tolerance was evaluated by assessing the presence of side effects, such as headache, dizziness, asthenia and digestive discomfort (flatulence, vomiting, abdominal distension and abdominal pain).

Surgical complications. Early (up to 30 days after surgery) surgical complications and late (until 6 months) surgical complications were recorded following the criteria of the American Society for Metabolic and Bariatric Surgery (ASMBS)[1]. Surgical complications were also categorized into major and minor complications following the same ASMBS criteria.

Sample size

Taking into account previous studies in this field [(9),(10)], 18 participants were required for each group to detect at least a 3% reduction in the liver volume between groups, with a standard deviation (SD) of 4%, a correlation of 0.7 between first and second measurements, with an α error of 0.05, a power of 0.80 and assuming a 5% of losses to follow-up.

Recruitment and Randomization

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Participants in the present study were recruited from March 2015 to July 2017 from the list of candidates for LRYGB and LSG after undergoing multidisciplinary supervision carried out by endocrinologists, surgeons, psychologists, anesthetists and dietitians.

After explaining the project, the researchers randomly assigned the volunteers who fulfilled the inclusion criteria to one of the two possible dietary interventions using an allocation sequence determined by a computer -generated randomization number table in 1:1 ratio.

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Data analysis

The normality of distribution of the continuous variables was assessed by the Kolmogorov-Smirnov test. To assess differences in continuous variables between groups, the unpaired T-Student test or the Mann Whitney U test were used for variables that were normally and non-normally distributed, respectively. The paired T-Student test and Wilcoxon test were used to evaluate within-group differences, as appropriate. We used the $\chi 2$ test to compare differences in categorical variables between groups. We used the Pearson correlation to assess correlations between weight loss and hepatic volume. A covariance analysis (ANCOVA) was used to determine which variables predicted hepatic volume change. The included variables were: gender, type of diet (VLCD and LCD), baseline hepatic volume, baseline BMI and hepatic enzymes (GOT, GPT, GGT). A linear regression model with weight loss after 6 months from the surgical intervention as dependent variable, and dietary intervention type, weight loss achieved at 21 days and the interaction term between them as independent variables was performed to evaluate if the degree of weight loss before bariatric surgery predicts the weight loss after bariatric surgery and if it differs between diets.

In order to take into account multiple-testing issue, we applied the Benjamin-Hochberg false discovery rate (FDR) procedure, considering the FDR <0.05 as statistically significant.

The continuous variables are given as mean±standard deviation and median (interquartile range: percentile 25–75), as appropriate, and categorical variables as numbers and percentages. The analyses were carried out with the package SPSS 20.0 (SPSS Statistics IBM®, Chicago, IL).

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RESULTS

Patient's baseline characteristics

Three hundred and eleven patients were eligible candidates for bariatric surgery, of which 46 were excluded because they did not meet the inclusion criteria, mainly due to having type 1 diabetes or taking oral anticoagulants; 3 did not want to participate, and 178 subjects were excluded because surgery could not be programmed due to lack of time in programming the operating theater (more than 5 weeks) or because the baseline computerized tomography could not be performed due to the short programming time. Therefore, of the 311 eligible participants, 86 were effectively randomized to the VLCD and LCD groups with 43 subjects in each group. There were no losses in the follow-up in the VLCD group; therefore, all the 43 cases were analyzed. In the LCD group, two patients dropped out: one due to renal failure (n=1) and one due to a traffic accident (n=1). Therefore, 41 subjects were analyzed in the LCD group. The detailed flow-chart of participants is shown in Figure 1.

The baseline characteristics of the participants are shown in Table 1. There were no significant differences between intervention groups for any of the parameters studied. The most prevalent comorbidity for the two groups was hypertension followed by dyslipidemia, obstructive sleep apnea syndrome and type 2 diabetes mellitus.

There were no significant differences between groups in terms of physical activity or sedentary time at baseline.

Hepatic Volume (Table 2).

With respect to baseline values, the hepatic volume decreased significantly in both intervention groups; however, there were no significant differences between groups. There were also no

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significant differences when the population was stratified by two BMI (> or < 50 Kg/m^2) categories.

Several correlations were made to determine the parameters that influenced the initial hepatic volume, showing a significant correlation between the baseline total body weight and BMI with the baseline hepatic volume (r = 0.498, adjusted P-value = 0.001 and r = 0.523, adjusted P-value=0.001, respectively). Using ANCOVA, the hepatic volume reduction during the intervention was directly related to the baseline liver volume (adjusted P-value =0.001) and the baseline BMI (adjusted P-value=0.001). However, results by type of dietary intervention (LCD vs VLCD) were not significant (adjusted P-value=0.196). A significant positive correlation was also found between the total weight lost and the hepatic volume reduction during the intervention (r = 415; adjusted P-value=0.001). When we stratified the population by the baseline hepatic volume (< 3L or ≥ 3L), a non-significant reduction of 18.8% and 18.0% for VLCD and LCD, respectively, was observed in those individuals with a baseline hepatic volume ≥ 3L (adjusted P-value=0.923 between groups differences), whereas a significant reduction of 14.4% and 11.3% was observed for those with a baseline liver volume less than 3L (adjusted P-value=0.409 between groups differences). Figure 2 shows changes in hepatic volume and % of total weight loss after a dietary intervention.

Body weight, body composition and blood pressure (Table 3)

Weight loss during the dietary intervention (at 21 days) was significantly higher in participants in the VLCD group than in the LCD group, representing a 5.8% and 4.2% of the total weight lost (TWL) (adjusted P-value=0.004). The TWL at 6 months from the baseline visit was 37.9±10.6% and 36.2±9.1 (adjusted P-value=0.451) for the VLCD and LCD groups,

respectively. Weight loss at 21 days predicted weight loss after 6 months of intervention. Specifically, 1 kg lost, regardless dietary intervention, predicted a weight loss of 0.79 kg after 6 months from the surgical intervention (adjusted P-value=0.04). However, when we analyzed the predicted weight loss at 6 months stratified by dietary intervention, no differences were observed (adjusted P-value=0.451).

There were no significant differences in changes in fat mass, lean mass or muscle mass between groups. Blood pressure significantly decreased in both intervention groups; however, no significant differences between groups were observed.

Changes in biochemical parameters (Tables 4 and 5)

Changes in serum glucose and insulin, glycosylated hemoglobin and HOMA-IR were not significantly different between groups, although there was a trend in the VLCD group participants to a greater decrease compared to those in the LCD group. Both groups showed a significant improvement in the lipid profile, with a major trend in the VLCD group. However, there were no significant differences between groups in relation to lipid profile and uric acid concentrations.

Although individuals in the VLCD and LCD group showed a significant decrease in the estimated glomerular filtration rate, there were no significant differences between groups in changes in renal function parameters. During the intervention, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased significantly in the VLCD group but there were no significant differences between groups.

The leukocyte and neutrophil counts significantly decreased during the two dietary interventions, whereas lymphocyte and monocytes only decreased significantly in the VLCD

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group. There were no significant differences between groups for any of the parameters of the white series studied. There were no significant changes between groups in terms of protein status and inflammation.

Dietary compliance and tolerance

The percentage of returned formula sachets was 96.7±6.8% and 97.0±7.4% (P = 0.875) for the VLCD and LCD groups, respectively. There was a 94% of participants with a high adherence to the intervention (≥80% of the sachets consumed) and 6% with low adherence (<80% of the sachets consumed).

The percentage of weight lost at 6 months of surgery was 28.8±5.4% in those individuals with high adherence (≥ 80%) and 27.5±12 in those with low adherence (<80%), P= 0.666 between high and low adherence. No differences in the rate of surgical complications were shown between those individuals with high or lower adherence to the intervention measured by the formula sachets returned P = 0.686. According to the number of extra food consumed during the intervention, there was a 95.3% of patients with very good or good adherence, 2.3% with regular, and 2.3% with poor in the VLCD group, and 92.7% with very good or good, 4.9% with regular, and 2.4% with bad adherence in the LCD group, without significant differences between intervention groups.

Regarding tolerance, a higher percentage of participants in the VLCD group had a feeling of dizziness during the first week (39.5% vs. 12%, adjusted P-value=0.008) and asthenia during the first two weeks of the intervention (48.8% vs. 17% in the first week and 37.2% vs 21% in the second week, adjusted P-value<0.05 for the VLCD and LCD groups respectively). There were no significant differences between groups in other recorded tolerance parameters.

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Perioperative complications and hospital stay (Table 6)

In Table 6 we report all the complications by type of surgery and intervention group. Three major and two minor early complications occurred in individuals in the VLCD group, whereas four major and one minor early complications were observed in participants in the LCD intervention. One and two major late complications were observed in individuals in the VLCD and LCD interventions, respectively. The surgical intervention initially proposed by the surgeon did not have to be changed due to hepatomegaly in any of the subjects. There were no complications due to liver bleeding in any of the study patients, and no death occurred in any of the randomized participants. The average hospital stay was 2.8±1.1 and 3.0±1.7 for the VLCD and LCD groups respectively without significant differences between groups.

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DISCUSSION

Weight loss before bariatric surgery is a common practice in many surgery clinics to reduce liver volume and help improve technical aspects of surgery. However, there have been no randomized controlled clinical trials that clearly demonstrate its benefits on the results of surgery. Our study is the only randomized study that compares the effect of a LCD diet and a VLCD diet before surgery on liver volume, anthropometrics, biochemical parameters, surgical complications, hospital stay and considering adherence and tolerance to the diet.

It is recognized that both LCD and VLCD diets are effective methods for reducing weight in the short term, but there is controversy about which is the best method for reducing liver volume. Our results show that the two diets significantly reduce liver volume (15.6% in the VLCD group and 12.3% in the LCD group), and that reduction was directly related to the baseline BMI and hepatic volume. Patients with a higher weight or BMI had a greater reduction in liver volume regardless of the type of dietary intervention performed. For the two dietary intervention groups, a 18% reduction of liver volume was shown in those patients with a baseline liver volume greater than 3 liters, whereas the liver volume reduction was 14.4% in the VLCD group and 11.3% in the LCD group in those patients with a baseline liver volume less than 3 liters.

Similar results were obtained by Colles et al. [9] after a VLCD diet for 12 weeks. In that study, a 13.8% reduction in liver volume was reported in those patients with a baseline liver volume lower than 2.8 liters versus 26.9 % in those with a baseline liver volume greater than 2.8 liters. These authors demonstrated that approximately 80% of the reduction occurs in the first two weeks of dietary caloric restriction. Other authors have also observed that the reduction in hepatic volume occurs mainly between 2 and 4 weeks after starting the intervention [5,10].

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Unfortunately, in our study we were unable to analyze when the liver reduction occurred because no repeated measurements of this parameter were scheduled during the dietary intervention.

The weight loss obtained by the participants in our study was similar to that obtained in similar participants of other studies after dietary caloric restrictions for 2 [11] or 4 weeks [12]. In a systematic review of preoperative dietary interventions to reduce the hepatic volume, a large variability in the caloric content (between 456 and 1520 Kcal), the type of diet administered and the intervention length (between 2 and 12 weeks) was reported between the studies [6]. In this systematic review, the BMI decreased between 5.1 and 12.6 kg/m^2, and the reduction in the hepatic volume was reported to be between 5 and 20% [6]. The authors of this systematic review highlight that an important limitation of the studies included is that the influence of VLCD and LCD on protein catabolism was not assessed [6]. In our study, patients on a VLCD achieved greater weight loss, although a non-significant larger decrease in lean mass and muscle mass was shown in this group compared to those on a LCD. Regarding the prealbumin levels, we found a significant decrease in both dietary intervention groups, although this reduction was not significantly different between them. Thus, it seems that in case of VLCD there is a greater tendency (not significant between groups) to reduce visceral proteins, as well as total proteins and albumin. However, this has not been associated to a higher rate of surgical complications or a longer hospital stay.

Pekkarinen et al. [13] analyzed the effect of a VLCD for 9 weeks on some immune-related parameters. Although they reported changes in some immune parameters, they concluded that the intervention did not seem to compromise the immune system. Despite the fact that the study of Pekkarinen et al., was more complete in terms of the parameters analyzed on the immune

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system, our results are in line with those found in reference to the significant decrease in lymphocytes in the VLCD group. It is important to highlight that we have studied two types of dietary intervention, and in our study, leukocyte and neutrophil counts decreased significantly in both groups while lymphocyte and monocytes only in the VLCD group, suggesting a non-significant trend to a greater reduction following this type of intervention. In our study, no significant differences were found between groups regarding glycemic or lipid profile, although it improved significantly after the two dietary interventions. Importantly, only the VLCD decreased significantly basal glycemia and LDL cholesterol after 21 days of intervention. Similar results, regarding lipid profile, were observed in the study conducted by Edholm et al., in 2015 after 28 days of dietary intervention [5].

In our study, the estimated glomerular filtration changed significantly during weight loss in the two intervention groups and creatinine levels only increased significantly in the VLCD group, not being these differences significant between groups. There was a significant increase in the AST and ALT values in the VLCD group, without significant differences between the groups. This could be explained by the high degree of cytolysis in those individuals on this diet. Edholm et al. [5] also found an increase in these transaminases after a LCD for 4 weeks. However, in the study by Alabadli et al. (16), both renal and hepatic related parameters did not significantly change after 30 weeks on a LCD.

Some studies have demonstrated a low adherence to the diet is based exclusively on commercial products [9,14,16]. In our study, adherence to the hypocaloric diet was very high in both intervention groups, although tolerance was significantly lower in those patients on a VLCD with a higher percentage of participants with dizziness and asthenia during the first two weeks of the intervention. These results are similar to those reported by Carbajo et al. [14] and

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Schouten et al. [16]. In the study by Faria et al. [11], patients on an exclusively liquid diet reported being hungrier than those who ate foods of normal consistency, although the adherence measured by ketosis was good and similar in both groups.

Regarding perioperative complications, Van Niuenhove et al. [7] reported a significantly lower number of cases of perioperative complications in those patients on a VLCD compared to a control group that did not take any other formula. Schouten et al. recently compared the effect of two types of VLCDs and did not report differences in the length of hospital stay or in the percentage of surgical complications. In our study, there were no significant differences in the number of complications between the two intervention groups. These complications appear to be directly related to the type of intervention more than the type of diet prescribed. Compared to those on a LSG, patients with a LRYGB had more complications, probably due to the greater complexity of the surgery. No complications directly related to the increase in liver volume were found in our study.

Our study has some limitations that need to be acknowledged. First, it was conducted in morbid obesity patients undergoing LRYGB or LSG surgery, and therefore, we cannot generalize to other populations (subjects with a BMI lower than kg/m^2) or patients undergoing other surgical techniques. Second, unfortunately, the difficulty perceived by the surgeon according to the type of intervention has not been evaluated objectively or subjectively in our study as have been done by other studies [7, 16]. Third, we do not have used a biomarker to check the intervention adherence, therefore we do not know with exactitude the degree of compliance with intervention as the participants live at home. However, we checked the compliance with the Optifast consumption after carefully checking the empty sachets in each visit. Finally, the two diets provided to the participants (VLCD and LCD) differed in terms of number of sachets

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provided and food allowed, which could affect the adherence and attrition, however the theoretically macronutrient content was estimated to be the same.

As strengths we need to highlight that, the target population of our study was very homogeneous in terms of age and degree of obesity; however, the most important strength of our study is the joint evaluation of the effect of dietary interventions on liver volume, body composition, biochemical parameters, surgical complications and hospital stay, while at the same time assessing tolerance and adherence to the diet.

Conclusions: Our results demonstrated for the first time, that compared to a LCD, a pre-operative 21-day intervention with VLCD is more effective in terms of reducing total body weight, although both diets are equally effective for reducing liver volume, which is important for improving the vision of the gastroesophageal area and reducing the susceptibility to bleeding. Moreover, both diets have the same rate of complications and hospital length stay. Further studies are needed to confirm these findings.

Source of funding: This study has been funded in part by Nestlé Health Science. This institution has no role in data collection, analysis or interpretation of the results nor has it influenced the publication of these results.

Conflict of Interest: Jordi Salas-Salvadó reports receiving a grant from Nestle thorough his Institution. The rest of authors declare that they have no conflict of interest.

Compliance with Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figure 1. Flow chart of participants

Figure 2. Changes in hepatic volume and % total weight loss after a VLCD or LCD.

TWL= total weight loss; HVL= hepatic volume loss; VLCD= very low calorie diet; LCD= low calorie diet. Results are expressed as mean ± standard deviation.

*: $p<0.05$ between groups

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Figure 1. Flow chart of participants

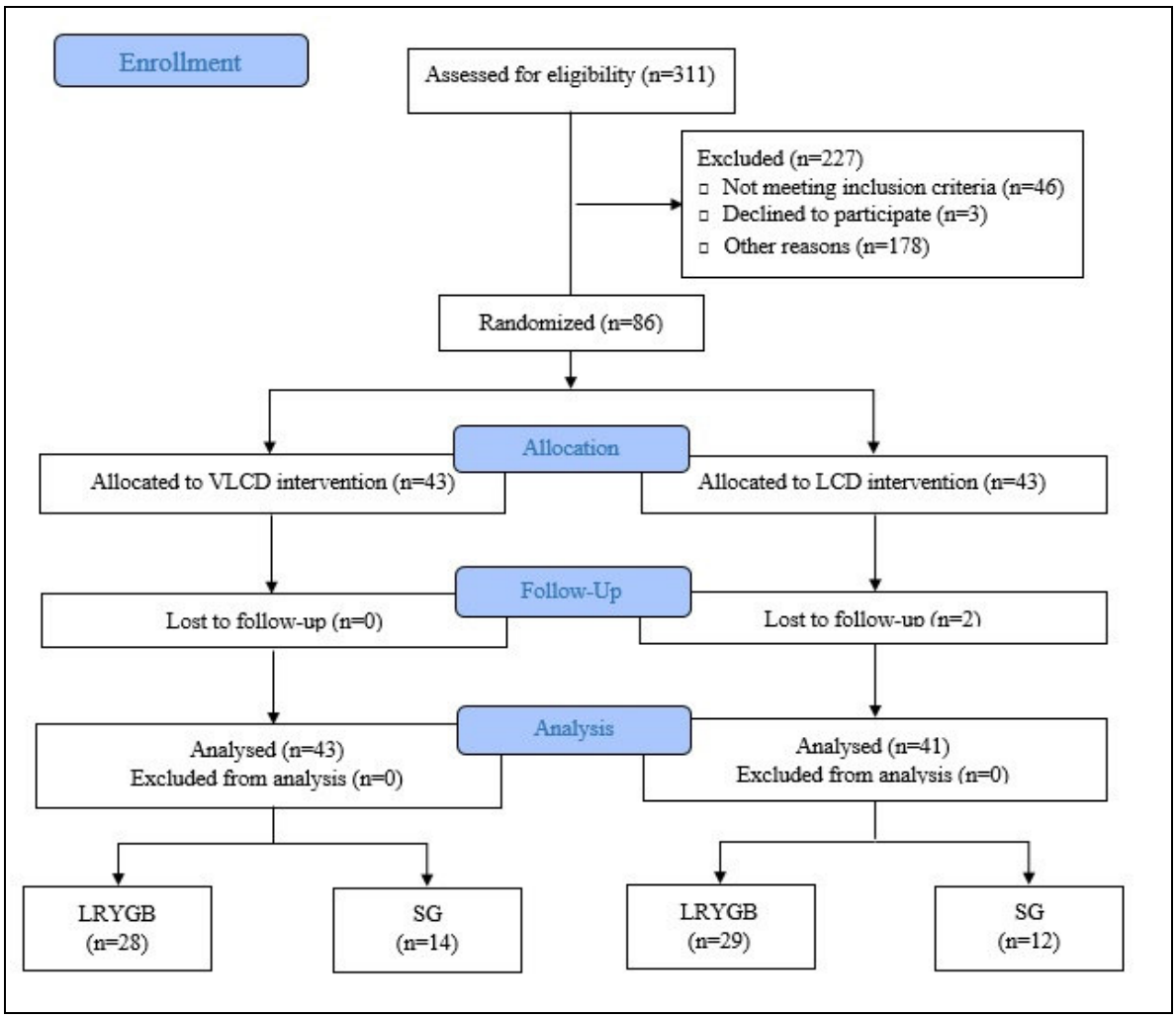

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Figure 2. Changes in hepatic volume and % total weight loss after a VLCD or LCD.

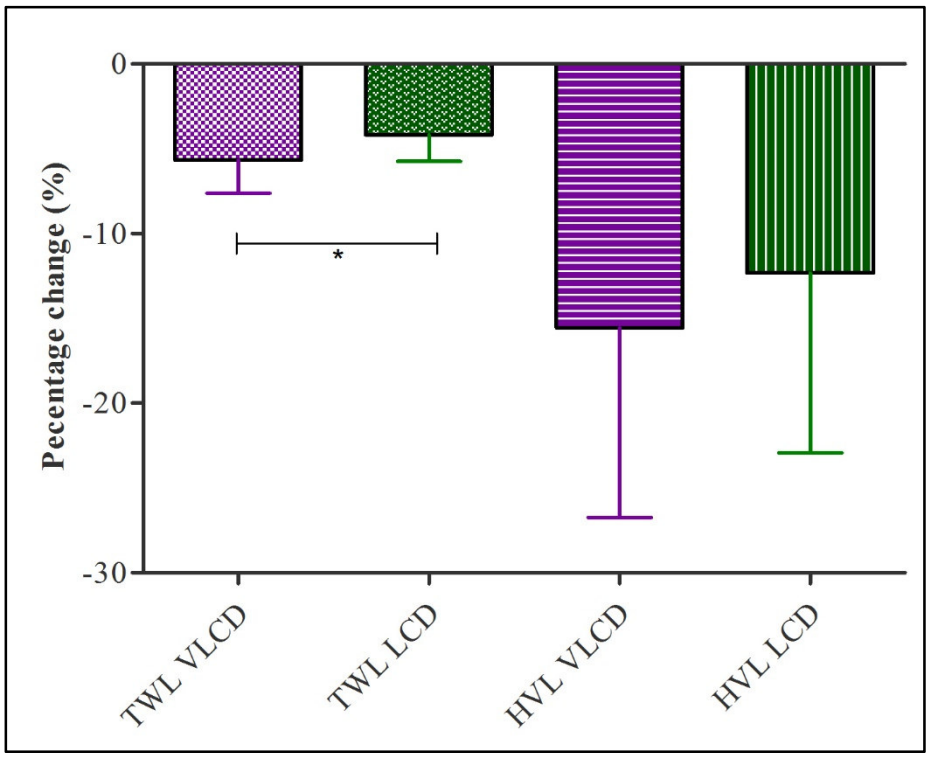

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Table 1. Descriptive characteristics of the participants at baseline

Parameters	**Group**	**VLCD**	**LCD**
	n=84	***n=43***	***n=41***
Gender, female (*n*/%)	63 (75%)	29 (67.5%)	34 (82.9%)
Age (years)	45.3±10.1	45.2±10.5	45.5±9.7
Weight (kg)	129.1±20.2	131.9±22.6	126.2±17.1
Height (cm)	165.1±8.4	166.7±9.4	163.4±6.8
Body mass index (kg/m^2)	47.3±5.2	47.3±5.3	47.2±5.0
Waist (cm)	135.8±15.1	137.3±16.5	134.2±13.5
SBP (mmHg)	147.8±24.3	145.8±30.0	149.7±17.6
DBP (mmHg)	91.8±12.5	91.4±13.2	92.2±12.1
Comorbidities			
Type 2 diabetes (*n*/%)	15 (17.9%)	11 (25.6%)	4 (9.8%)
Dyslipidemia (*n*/%)	35 (41.7%)	20 (46.5%)	15 (36.6%)
Hypertension (*n*/%)	41 (48.8%)	24 (55.8%)	17 (41.5%)
OSAS (*n*/%)	19 (22.6%)	11 (25.6%)	8 (19.5%)

Abbreviations: VLCD, very low calorie diet; LCD, low calorie diet; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; OSAS, obstructive sleep apnea syndrome; Results are expressed as mean ± standard deviation or number and percentage of individuals.

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Table 2. Changes in hepatic volume before and after a VLCD or LCD.

Parameters	Baseline (cc)	Final	Change (cc)	Change (%)	Intra groups	
Total participants					**P-value**	**Adjusted P-value†**
VLCD (*N*=34)	2653±654	2208±458	-445±432	-15,6±11,2	<0.001	0.045
LCD (*N*=38)	2600±833	2268±775	-332±340	-12,3±10,6	<0.001	0.045
P-value*	0.768	0.873	0.222	0.212		
Adjusted P-value†	0.923	0.923	0.409	0.409		
Participants with a hepatic volume < 3L						
VLCD (*N*=25)	2355±320	2010±303	-345±226	-14.4±9.1	<0.001	0.045
LCD (*N*=32)	2342±401	2071±360	-271±222	-11.3±8.5	<0.001	0.045
P-value	0.898	0.503	0.227	0.190		
Adjusted P-value	0.923	0.696	0.409	0.409		
Participants with a hepatic volume > 3 L						
VLCD (*N*=9)	3480±643	2757.2±360.3	-723±707	-18.8±15.9	0.015	0.054
LCD (*N*=6)	3975±1203	3317±1439	-657±632	-18.0±18.3	0.052	0.156
P-value	0.316	0.390	0.857	0.923		
Adjusted P-value	0.0517	0.585	0.923	0.923		

Abbreviations: VLCD, very low calorie diet; LCD, low calorie diet; cc: cubic centimeters; NS, not significant.

Results are expressed as mean ± standard deviation. To determine differences between groups a U was applied.

*: P value for between-group differences.

†The Benjamin-Hockberg procedure for multiple-testing was used to calculate adjusted P-values, considering an FDR <0.05 as significant.

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Table 3. Changes in weight, body composition and blood pressure after 21 days of VLCD or LCD interventions.

Parameters	Diet	Baseline	Final	Change	Intra groups	
					P-value	Adjusted P-value†
Weight (kg)	VLCD (*n*=42) LCD (*n*=41) P-value* Adjusted P-value†	131.2±22.4 126.2±17.1 0.257 0.402	123.6±21.0 120.8±16.0 0.511 0.608	-7.65±2.66 -5.36±2.21 <0.001 0.002	<0.001 <0.001	0.002 0.002
TWL (%)	VLCD (*n*=42) LCD (*n*=41) P-value* Adjusted P-value†	131.2±22.4 126.2±17.1 0.257 0.402	123.6±21.0 120.8±16.0 0.511 0.608	-5.81±1.71 -4.19±1.55 <0.001 0.002	<0.001 <0.001	0.002 0.002
BMI (kg/m^2)	VLCD (*n*=42) LCD (*n*=41) P-value* Adjusted P-value†	47.2±5.4 47.2±5.0 0.984 0.984	44.5±5.6 45.2±4.8 0.504 0.068	-2.73±0.82 -2.01±0.81 <0.001 0.002	<0.001 <0.001	0.002 0.002
Waist circumference (cm)	VLCD (*n*=42) LCD (*n*=41) P-value* Adjusted P-value†	137.2±16.7 134.2±13.5 0.388 0.530	131.2±15.3 129.5±11.0 0.576 0.670	-5.95±7.13 -4.77±7.01 0.453 0.581	<0.001 <0.001	0.002 0.002
Fat (kg)	VLCD (*n*=42) LCD (*n*=40) P-value* Adjusted P-value†	66.2±16.6 63.7±14.4 0.605 0.681	62.0±15.6 61.1±11.0 0.752 0.800	-4.11±4.43 -2.67±3.14 0.094 0.188	<0.001 <0.001	0.002 0.002
Lean mass (Kg)	VLCD (*n*=42) LCD (*n*=40) P-value* Adjusted P-value†	65.0±15.2 61.6±7.1 0.207 0.379	61.5±13.0 58.9±6.9 0.247 0.402	-3.52±4.59 -2.78±3.32 0.408 0.537	<0.001 <0.001	0.002 0.002
Muscle mass (Kg)	VLCD (*n*=42) LCD (*n*=40) P-value* Adjusted P-value†	61.8±14.5 58.5±6.8 0.202 0.379	58.4±12.4 55.9±6.5 0.247 0.402	-3.38±4.44 -2.65±3.17 0.392 0.530	<0.001 <0.001	0.002 0.002
Water (Kg)	VLCD (*n*=33) LCD (*n*=36) P-value* Adjusted P-value†	48.3±11.4 45.5±6.1 0.212 0.380	45.3±9.9 43.4±5.8 0.360 0.514	-3.08±1.90 -2.08±2.21 0.050 0.104	<0.001 <0.001	0.002 0.002

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SBP (mmHg)	VLCD (*n*=38) LCD (*n*=40) P-value* Adjusted P-value†	149.1±21.9 149.7±17.8 0.902 0.940	139.4±14.4 141.5±17.0 0.286 0.433	-9.71±21.85 -8.23±17.05 0.738 0.800	0.009 <0.001	0.020 0.002
DBP (mmHg)	VLCD (*n*=38) LCD (*n*=40) P-value* Adjusted P-value†	91.2±13.3 92.4±12.1 0.731 0.800	84.7±10.4 86.06±11.5 0.342 0.503	-6.50±13.00 -6.36±10.83 0.960 0.980	0.004 <0.001	0.010 0.002

Abbreviations: VLCD, very low calorie diet; LCD, low calorie diet; BMI, body mass index; TWL, total weight loss; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

Results are expressed as mean ± standard deviation. To determine differences between groups a t-student test was applied.

*: P value for between-group differences.

†The Benjamin-Hockberg procedure for multiple-testing was used to calculate adjusted P-values, considering an FDR <0.05 as significant.

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Table 4. Changes in glycemic and lipid profiles after 21 days of VLCD or LCD interventions.

Parameters	Diet	Baseline	Final	Change	Intra groups	
Glucose profile					**P-value**	**Adjusted P-value†**
Serum glucose (mg/dL)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	122.6±49.8 102.7±33.5 0.032 0.068	97.3±15.4 95.7±19.2 0.670 0.699	-25.3±45.3 -7.0±19.9 0.021 0.052	0.001 0.032	0.001 0.068
HbA_1c (%)	VLCD (*n*=43) LCD (*n*=39) P-value* Adjusted P-value†	6.5±1.7 5.9±1.4 0.597 0.655	6.01±1.2 5.7±1.2 0.270 0.374	-0.5±0.6 -0.2±0.3 0.037 0.072	<0.001 <0.001	<0.001 <0.001
Serum insulin (mcUI/mL)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	23.2±14.1 19.0±10.5 0.123 0.213	15.0±8.4 15.0±9.0 0.922 0.922	-8.2±10.5 -4.0±6.5 0.033 0.068	<0.001 <0.001	<0.001 <0.001
HOMA-IR	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	5.4 (3.4-8.6) 4.5 (2.9-6.7) 0.074 0.133	3.25 (2.1-4.3) 3.0 (1.9-4.4) 0.424 0.545	-2.4(-0.9-(-3.4)) -1.3(+0.01-(-2.2) 0.019 0.050	<0.001 <0.001	<0.001 <0.001
Lipid profile						
Total Cholesterol (mg/dL)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	182.0±30.8 190.9±34.9 0.233 0.338	158.3±30.6 172.7±33.0 0.043 0.081	-23.7±23.8 -18.3±21.1 0.274 0.374	<0.001 <0.001	<0.001 <0.001
HDL-cholesterol (mg/dL)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	47.1±10.1 53.0±12.1 0.013 0.037	39.4±9.5 46.3±9.9 0.002 0.001	-7.7±6.7 -6.8±7.6 0.547 0.630	<0.001 <0.001	<0.001 <0.001
LDL-cholesterol (mg/dL)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	106.6±26.3 110.9±31.6 0.560 0.630	95.2±30.8 104.6±29.5 0.162 0.270	-11.4±17.33 -6.6±17.1 0.198 0.297	<0.001 0.022	<0.001 0.052
Triglycerides (mg/dL)	VLCD (*n*=43) LCD (*n*=41) P-value* Adjusted P-value†	126 (97-184) 119 (91-172) 0.450 0.557	107.0 (86-132) 103 (79.5-132.5) 0.458 0.557	-21(+6-(-55)) -13(+7.5-(-50.5) 0.668 0.699	0.001 0.002	0.001 0.006

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Uric acid (mg/dL)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	5.90±1.48 5.49±1.22 0.193 0.297	6.0±1.7 6.9±8.9 0.508 0.602	+0.06±1.23 +1.39±8.79 0.328 0.434	0.179 0.683	0.288 0.699

Abbreviations: VLCD, very low calorie diet; LCD, low calorie diet; HbA1c, glycosylated hemoglobin; HDL, High-density lipoprotein; LDL, low density lipoproteins.

Parameters following a normal distribution are expressed as mean ± standard deviation and median (interquartile range: 25-75). To determine differences between groups a t-student test was applied as well as a Mann Whitney test. The Wilcoxon test was used for nonparametric paired data.

*: P value for between-group differences.

†The Benjamin-Hockberg procedure for multiple-testing was used to calculate adjusted P-values, considering an FDR <0.05 as significant.

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Table 5. Changes in biochemical parameters after 21 days of VLCD or LCD interventions.

Parameters	Diet	Baseline	Final	Change	Intra groups	
Renal function					**P-value**	**Adjusted P-value†**
Urea (mg/dL)	VLCD (*n*=43) LCD (*n*=39) P-value* Adjusted P-value†	33.4±8.8 35.64±7.3 0.301 0.426	31.3±12.0 36.05 0.038 0.100	-2.1±9.9 +0.4±6.2 0.185 0.308	0.749 0.323	0.832 0.439
Creatinine (mg/dL)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	0.71±0.19 0.74±0.11 0.440 0.522	0.76±0.19 0.77±0.12 0.905 0.933	+0.05±0.11 +0.02±0.06 0.218 0.347	0.005 0.020	0.022 0.067
eGFR (ml/min/1.7)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	106.6±18.1 100.1±13.5 0.067 0.147	101.4±19.6 97.8±14.7 0.354 0.441	-5.2±10.0 -2.0±6.8 0.095 0.200	<0.001 <0.001	0.001 0.001
Hepatic function and liver enzimes						
AST (UI/L)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	22.2±12.4 19.8±5.7 0.251 0.390	29.1±11.2 22.7±7.7 0.003 0.016	+7.0±9.0 +2.9±7.4 0.028 0.078	<0.001 0.017	0.001 0.062
ALT (UI/L)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	27.5±22.6 24.4±11.1 0.396 0.478	39.8±26.4 28.7±15.5 0.023 0.070	+12.3±19.8 +4.2±12.8 0.032 0.086	<0.001 0.043	0.001 0.108
GGT (UI/L)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	40.2±49.7 28.5±18.7 0.153 0.275	28.4±26.5 23.8±16.4 0.339 0.439	-11.7±33.5 -4.7±9.8 0.206 0.335	0.027 0.004	0.078 0.02
Leukocyte count						
Leukocytes (x10^3/ul)	VLCD (*n*=43) LCD (*n*=39) P-value* Adjusted P-value†	7.84±2.05 7.47±1.89 0.349 0.441	6.2±1.5 6.60±1.6 0.296 0.426	-1.60±1.27 -0.87±1.51 0.020 0.067	<0.001 0.001	0.001 0.001
Neutrophils (x10^3/ul)	VLCD (*n*=43) LCD (*n*=39) P-value* Adjusted P-value†	4.72±1.50 4.74±1.60 0.945 0.959	3.6±1.1 4.09±1.27 0.059 0.133	-1.14±0.92 -0.66±1.23 0.045 0.109	<0.001 0.002	0.001 0.012

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Lymphocytes (x10^3/ul)	VLCD (*n*=43) LCD (*n*=39) P-value* Adjusted P-value†	2.26±0.66 2.00±0.49 0.051 0.119	1.96±0.5 1.84±0.49 0.277 0.422	-0.30±0.40 -0.15±0.40 0.100 0.200	<0.001 0.022	0.001 0.070
Monocytes (x10^3/ul)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	0.55±0.18 0.51±0.15 0.498 0.571	0.49±0.1 0.49±0.14 0.906 0.932	-0.06±0.12 -0.29±0.10 0.148 0.273	0.001 0.097	0.001 0.200
Protein status and inflammation						
Total proteins (g/dL)	VLCD (*n*=43) LCD (*n*=41) P-value* Adjusted P-value†	7.12±0.35 7.12±0.41 0.964 0.964	7.25±0.37 7.19±0.41 0.514 0.580	+0.13±0.30 +0.05±0.34 0.304 0.426	0.009 0.336	0.037 0.439
Albumin (g/dL)	VLCD (*n*=43) LCD (*n*=41) P-value* Adjusted P-value†	.34±0.23 4.32±0.25 0.882 0.933	4.46±0.24 4.38±0.26 0.135 0.256	+0.13±0.22 +0.05±0.22 0.113 0.220	0.001 0.184	0.001 0.308
Prealbumin (mg/dL)	VLCD (*n*=43) LCD (*n*=40) P-value* Adjusted P-value†	23.75±5.51 23.55±4.04 0.849 0.914	20.74±4.85 21.56±5.27 0.466 0.544	-3.01±3.97 -2.10±4.49 0.327 0.439	<0.001 0.005	0.001 0.022
CRP (mg/dL)	VLCD (*n*=43) LCD (*n*=41) P-value* Adjusted P-value†	0.80 (0.44-1.30) 0.70 (0.50-1.40) 0.805 0.880	0.6 (0.4-1.1) 0.8 (0.5-1.3) 0.160 0.280	-0.10(+0.10-(-0.60) -0.05(0.18-(-0.33)) 0.292 0.423	0.010 0.359	0.039 0.441

Abbreviations: VLCD, very low calorie diet; LCD, low calorie diet; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gammaglutamyltransferase; CRP, C-reactive protein.

Parameters following a normal distribution are expressed as mean ± standard deviation and median (interquartile range: 25-75). To determine differences between groups a t-student test was applied as well as a Mann Whitney test. The Wilcoxon test was used for nonparametric paired data.

*: P value for between-group differences.

†The Benjamin-Hockberg procedure for multiple-testing was used to calculate adjusted P-values, considering an FDR <0.05 as significant.

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Table 6. Surgical complications from the intervention until 6 months

	VLCD ***N*=42**	**LCD** ***N*=41**
Early complications		
Major	Prolonged hospitalization (> 7 days): intra-abdominal collection. (LRYGB)	Prolonged hospitalization (> 7 days): infection of the wound by MARSA that required antibiotic treatment and hospitalization of more than seven days. (LRYGB)
	Surgical site infection (superficial, deep or organ space) requiring debridement or washout in the operating room or percutaneous intervention. (LRYGB)	Prolonged hospitalization (> 7 days): small gastrointestinal anastomosis leak that did not require reoperation. (LRYGB)
	Venous thrombotic event requiring administration of anticoagulant: bilateral pulmonary thromboembolism that required anticoagulant treatment. (LRYGB)	Prolonged hospitalization (> 7 days): prolonged stay in the intensive care unit for pyelonephritis caused by urinary infection. (SG)
		Gastrointestinal hemorrhage requiring transfusion. (LRYGB)
Minor	Urinary tract infection managed with antibiotics. (LRYGB)	Urinary tract infection managed with antibiotics. (LRYGB)
	Symptomatic cholelithiasis. (LRYGB)	
Late complications		
Major	Gastric sleeve stenosis/obstruction requiring revision to a gastric bypass: gastric torsion. (SG)	Gastrointestinal hemorrhage requiring transfusion. (LRYGB)
		Cholecystectomy. (LRYGB)
Minor	No minor or late complications occurred	No minor or late complications occurred

Abbreviations: VLCD, very low calorie diet; LCD, low calorie diet