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ORIGINAL CONTRIBUTIONS

Four Weeks of Preoperative Omega-3 Fatty Acids Reduce Liver Volume: a Randomised Controlled Trial

Nathalie Bakker[1,2,3] · Rick S. van den Helder[1,2] · Remy W. F. Geenen[2] · Michiel A. Hunfeld[1] · Huib A. Cense[1] · Ahmet Demirkiran[1] · Alexander P. J. Houdijk[1,2,3]

Abstract

Purpose Weight loss before bariatric surgery with a low-calorie diet (LCD) has several advantages, including reduction of liver volume and an improved access to the lesser sac. Disadvantages include performing surgery in a state of undernutrition, side effects, costs and patient compliance. Omega-3 fatty acids may serve as an alternative to reduce liver steatosis.

Materials and Methods A randomised controlled open-label trial was done to compare the effects of a LCD with Modifast (800 kcal/day) during 2 weeks with 2 g of omega-3 fatty acids a day and a normal diet (2000 kcal/day) during 4 weeks. Total liver volume (TLV) and volume of the left liver lobe (LLL), visceral fat area (VFA) and muscle area (SMA) at the L3–L4 level were measured with MRI before and after preoperative treatment.

Results Sixty-two morbidly obese women undergoing laparoscopic Roux-en-Y gastric bypass surgery (LRYGB) were recruited. In both groups, there was a significant decrease in LLL, TLV and VFA. For LLL and TLV reduction, the LCD had a significantly larger effect ($p < 0.05$). Only in the LCD group was there a significant decrease in SMA with significantly more side effects and worse compliance.

Conclusion Both the LCD and omega-3 diet reduced LLL, TLV and VFA. The LCD outperformed the omega-3 diet in LLL and TLV reduction, but induced significant loss of SMA and had worse compliance due to more side effects. Omega-3 fatty acids may provide a safe and more patient-friendly alternative for a LCD and further research is indicated.

Trial Registration The study is registered at www.clinicaltrials.gov (NCT02206256).

Keywords Laparoscopic Roux-en-Y gastric bypass · Liver volume · Visceral fat · Muscle mass · Low calorie diet · Omega-3 fatty acids

Introduction

Laparoscopic Roux-en-Y gastric bypass surgery (LRYGB) is a successful method to reduce overweight and metabolic complications in morbidly obese subjects [1]. During LRYGB, the technical approach to the lesser sac may be complicated by an enlarged fatty left liver lobe that may be injured on manipulation. To reduce liver volume, low-calorie diets for

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✉ Nathalie Bakker
nbakker@rkz.nl

Rick S. van den Helder
rsvandenhelder@rkz.nl

Remy W. F. Geenen
r.w.f.geenen@nwz.nl

Michiel A. Hunfeld
mhunfeld@rkz.nl

Huib A. Cense
hcense@rkz.nl

Ahmet Demirkiran
ademirkiran@rkz.nl

Alexander P. J. Houdijk
a.p.j.houdijk@nwz.nl

[1] Department of Surgery, Red Cross Hospital Beverwijk, Beverwijk, Netherlands

[2] Department of Surgery, Northwest Clinics Alkmaar, Alkmaar, Netherlands

[3] Department of Surgery, VU Medical Center Amsterdam, Amsterdam, Netherlands

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several weeks have been included in the preoperative workup. However, several weeks on a low-calorie diet may induce a state of undernutrition with unwanted loss of lean body mass, which is associated with poorer outcomes after surgery [2]. Other disadvantages of a low-calorie diet include lack of patient compliance and side effects like nausea/vomiting, constipation, loose stools/diarrhoea, hunger and a craving for something to chew [3–6].

Omega-3 fatty acids may be an alternative to the low-calorie diets to reduce liver volume. The fatty liver is associated with excessive intake of omega-6 fatty acids and a deficiency of polyunsaturated omega-3 fatty acids. Omega-3 fatty acid supplementation improves liver fat and serum markers of hepatic damage and dyslipidaemia in several clinical studies in children and adults [7]. In addition, preclinical studies suggest a modulating role of omega-3 fatty acids in hepatic inflammation and fibrosis [7]. Indeed, Ianelli et al. showed that supplementation of omega-3 fatty acids can reduce left liver lobe volume in morbidly obese patients in an uncontrolled pilot study.

In the present randomised controlled study, the effect of the standard preoperative low-calorie diet (LCD) was compared to that of a normal diet supplemented with omega-3 fatty acids on MRI liver volume and body composition in morbidly obese women undergoing LRYGB.

Methods

Study Design

This study was set up as a randomised, parallel group, controlled, open-label clinical trial with a 1:1 allocation ratio. Primary endpoint was the volume of the left liver lobe measured with MRI after treatment with omega-3 fatty acids or a low-calorie diet in the preoperative phase before LRYGB. Secondary endpoints were patient evaluation of pretreatment and assessment of the approach of the lesser sac by the surgeon, MRI muscle mass and visceral fat. The study was approved by the local regional Medical Ethics Committee of the VU Medical Center in Amsterdam and conducted according to the Declaration of Helsinki (as revised in 1983). Written informed consent was obtained from all patients. The study is registered at www.clinicaltrials.gov (NCT02206256).

Study Population

Inclusion criteria were as follows: female patients with morbid obesity, ages 18–65 years, scheduled to undergo LRYGB and able to fit in the MRI (< 220 kg and < 130 cm waist circumference). Exclusion criteria were as follows: pregnancy, previous bariatric surgery, diabetes mellitus type 1, current inflammatory disease that required anti-inflammatory or immune-modulating drugs (including NSAIDs, prednisone, methotrexate, monoclonal antibodies), current infectious or malignant disease and contraindications for MRI or omega-3 fatty acids. Only female patients were included in order to maintain group uniformity and because more than 80% of the patients that prepare for bariatric surgery at the Dutch Obesity Clinic are female.

Control Group

The control group received a preoperative LCD as is the standard care policy of the Dutch Obesity Clinic. Patients started 2 weeks prior to the day of surgery with a diet based on Modifast Shakes (or comparative diet shakes). Breakfast, lunch and dinner were replaced by a shake of 200 kcal. In addition, patients could eat a maximum of 1 portion of fruit (like an apple or orange) and 1 portion of a clear broth per day. Patients were allowed to eat cooked vegetables (except for legumes, corn, beetroot and avocado), raw vegetables (cucumber, tomatoes, celery) and unlimited water, tea, coffee (no milk or sugar added) and sugar-free soda. With this diet, a daily intake of about 800 kcal was pursued.

Intervention Group

The intervention group received omega-3 fatty acid capsules, 2 capsules a day during the last 4 weeks before surgery. Each capsule of 1000 mg contains 840 mg ethyl esters of EPA (460 mg) and DHA (380 mg) (Teva BV, the Netherlands). Patients were instructed to follow a 'normal, healthy diet' based on an average of 2000 kcal/day for women alongside the capsules. For a detailed description of the dietary advices, see attachment 1.

Randomisation

Patients were randomly assigned using a sealed envelope system that was created with a randomisation list from www.sealedenvelope.com. After written informed consent was obtained, the treatment allocation was revealed and the appointments for MRI and blood samples (2 or 4 weeks schedule) were planned.

MRI Body Composition Measurements

All patients had an abdominal MRI scan before they started the pretreatment and a second scan within 1–3 days prior to surgery. All patients were scanned in a 70-cm-diameter bore 1.5-T scanner (Magnetom Espree, Siemens Healthineers, Zoetermeer, the Netherlands). For measurements of volume of the left liver lobe and total liver volume, we used the software application Argus viewer (Siemens Healthineers, the Netherlands). We selected all MRI slides that showed part of

the liver and we traced the appropriate area on each slide by hand. The left liver volume (LLV) was measured as segments II, III, IVa and IVb (medial of the central liver vein). We excluded the inferior vena cava, the gallbladder and the fat along the falciform ligament. Total liver volume (TLV) was calculated by multiplying total area with the slice thickness. An axial T1-weighted gradient echo (GRE) sequence throughout the entire liver was used with the following parameters: TR 60 ms, TE 2.38 ms, flip angle 70°, FOV 430 mm, matrix 256 × 90, slice thickness 7 mm with a 1.4-mm gap. In order to determine the plane between the right and left liver lobes on the axial slices more precisely, an additional coronal T1-weighted GRE sequence throughout the entire liver was performed. Parameters were the same as the axial sequence, except for TR 49 ms and slice thickness 8 mm with a gap of 1.6 mm.

Visceral fat area (VFA) and skeletal muscle area (SMA) from a single MRI slice at the L3–L4 disk level were measured with the Slice-o-matic software from TomoVision. For this measurement, an axial T1-weighted GRE sequence containing 8 slices around discus L3–L4 was performed: TR 34 ms, TE 2.38 ms, flip angle 70°, FOV 430 mm, matrix 256 × 90, slice thickness 7 mm with a 7-mm gap. The measurements were done by an independent radiologist who was blinded for treatment allocation.

Interviews

Patients were interviewed on the day of surgery to evaluate the amount of side effects and how this had affected compliance with the diet. The side effects were defined as follows: bad taste, hunger, nausea/vomiting, diarrhoea and constipation based on patient's interpretation, compared to the period before the study. In addition, patients were asked if they experienced difficulty complying with the treatment and how often they did not follow the diet or skipped an omega-3 capsule. The surgeons were interviewed during surgery to evaluate the liver and the approach of the lesser sac. The liver was evaluated for enlargement and steatosis and the approach of the lesser sac and manipulation of the liver were also evaluated. The surgeon was unaware of the treatment allocation. The interviewer was not blinded to the intervention.

Sample Size Calculation

Pretreatment with a 4-week supplementation of omega-3 fatty acids showed a reduction of 20% in volume of the left hepatic lobe in 20 patients [8]. Assuming a reduction of 20% in the omega-3 fatty acid group and a baseline LLV of 598 cm^3 would imply a difference (after intervention) between the two groups of 90 cm^3. To detect this difference with an alpha of 0.05 and a power of 80% using a standard deviation of 118, 28 patients per group would be necessary. Assuming a drop-out rate of 10%, a total number of 62 was included.

Statistical Analysis

The intention to treat (ITT) population consists of all patients that are randomised and have a score on the primary outcome variable irrespective of being treated according to the protocol. The per protocol (PP) population comprises those patients of the ITT population who are treated according to the protocol. Depending on the distribution (normal or not), data were described as a mean with a standard deviation or as medians with an interquartile range. The groups were compared with the independent samples *t* test in case of a normal distribution or the Mann-Whitney *U* test in case of a non-normal distribution. For repeated measures, a mixed model analysis was done to compare the groups on the consecutive time points with a correction for baseline values. Data were statistically analysed using SPSS 20.0 or higher for Windows. A p value of 0.05 or less was considered statistically significant.

Results

The inclusion period was from November 2014 until March 2016. The data of the last follow-up visits 6 months after surgery were collected in November 2016. In Fig. 1, an inclusion flowchart of the study is shown. The intention to treat and per protocol groups are equal because no additional patients had to be excluded for per protocol analysis.

Baseline and Clinical Characteristics

In Table 1, the baseline and clinical characteristics of the intention to treat groups are shown. There were no significant differences between the groups. There were also no differences in weight or BMI after preoperative treatment between the groups. BMI changed from 41.4 to 39.5 in the LCD group and from 43.0 to 42.6 in the omega-3 group after preoperative treatment ($p = 0.367$).

MRI Body Composition Measurements (Reviewer no. 4, Comment no. 1)

In Table 2, MRI body composition is shown. In Fig. 2, examples of the measurements and body composition are shown. In both groups, LLV decreased significantly: LCD group from 593 (182) to 527 (182) ml, $p = 0.000$, and omega-3 group from 557 (346) to 535 (326) ml, $p = 0.049$. In the LCD group, there was a significantly larger decrease in LLL than in the omega-3 group: − 104 (139) ml vs. − 39 (153), $p = 0.025$. There was also a significant decrease in TLV in both groups: LCD group from 2137 (553) to 1866 (416) ml, $p = 0.000$, and

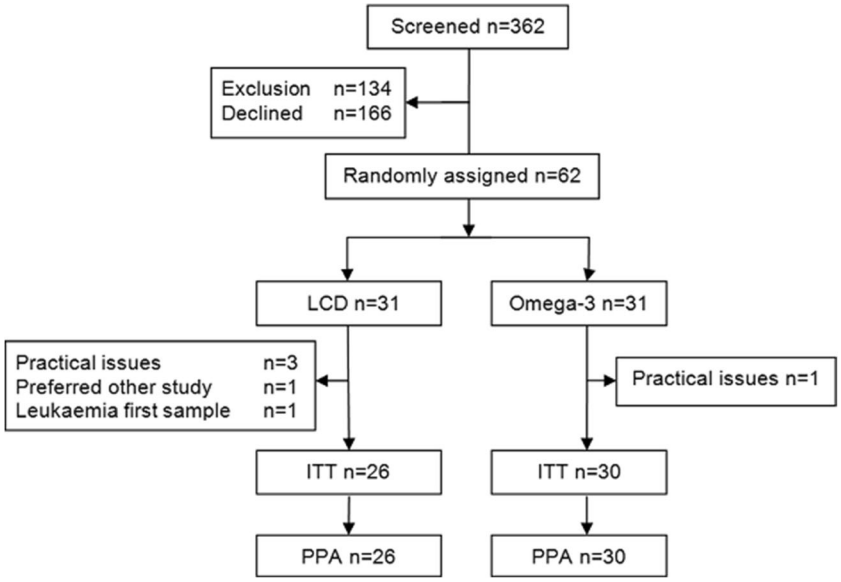

Fig. 1 Flowchart

omega-3 group from 2010 (528) to 1861 (696) ml, $p = 0.004$. In the LCD group, there was a significantly larger decrease in TLV than in the omega-3 group: − 269 (287) ml vs. 127 (249) ml, $p = 0.004$. In both groups, there was a significant decrease in VFA: LCD group from 213 (117) to 204 (117) cm^2, $p = 0.000$, and omega-3 group from 186 (146) to 184 (121) cm^2, $p = 0.002$. In the LCD group, there was a significant decrease in SMA from 160 (28) to 157 (28) cm^2, $p = 0.000$, that was not seen in the omega-3 group, 153 (32) vs. 153 (31) cm^2.

Interviews

The results of the patient interviews are shown in Table 3. There were several significant differences between the groups. In the LCD group, patients had more complaints about the taste and persistent hunger/appetite, had more side effects (diarrhoea, constipation) and more often reported difficulty complying with the diet. The results of the surgeon interview are shown in Table 4. The incidence of a difficult manipulation of the liver and/or a difficult access of the lesser sac was seen in 4 patients, 1 in the LCD group and 3 in the omega-3 group ($p = 0.615$). In all four patients, the LRYGB was executed without complications. The liver was enlarged with a blunt edge in 31% of the LCD group and 38% of the omega-3 group ($p = 0.642$). In 39% of the LCD group and 33% of the omega-3 group, $p = 0.690$, the liver was fatty with yellow discoloration.

Follow-up 6 Months After Surgery

In both groups, there was a significant decrease in BMI after LRYGB: LCD group BMI 41 (6) vs. 32 (7), $p = 0.000$;

Table 1 Baseline and clinical characteristics

	LCD ($n = 26$)	Omega-3 ($n = 30$)	p value
Age (years)	44 (18)	49 (37)	0.278
Weight (kg)	117 (31)	121 (19)	0.301
BMI (kg/m^2)	41 (6)	43 (6)	0.669
Diabetes (%)	7 (27)	4 (13)	0.202
Dyslipidaemia (%)	5 (19)	8 (27)	0.511
Hypertension (%)	10 (39)	11 (37)	0.890
Blood pressure systolic	130 (41)	150 (30)	0.133
Blood pressure diastolic (mmHg)	85 (14)	90 (15)	0.053
Hospital stay (days)	1 (1–5)	1 (1–8)	0.677
	Complications (%)		
SSI with abscess	0	1 (3.4%)	1.000
Urinary tract infection	1 (3.8%)	0	0.473

Values are presented as median (interquartile range) or percentage except for hospital stay (median with total range)

Table 2 MRI body composition measurements

		LCD ($n = 26$)	Omega-3 ($n = 30$)	p value
LLL	T1	593 (182, 546)	557 (346, 1299)	0.554
	T2	527 (182, 461)**	535 (326, 1211)*	0.366
	Delta	− 104 (139, 250)	− 39 (153, 347)	0.025
TLV	T1	2137 (553, 1533)	2010 (528, 2656)	0.662
	T2	1866 (416, 1449)***	1861 (696, 2660)**	0.341
	Delta	− 269 (287, 632)	− 127 (249, 1041)	0.004
VFA	T1	213 (117, 395)	186 (146, 304)	0.686
	T2	204 (117, 382)***	184 (121, 300)***	0.791
	Delta	− 7.9 (14, 62)	− 5.6 (19, 46)	0.900
SMA	T1	160 (28, 100)	153 (32, 102)	0.251
	T2	157 (28, 104)***	153 (31, 113)	0.811
	Delta	− 3.0 (3.8, 16)	0.6 (3.4, 18)	0.000

Values between groups were compared with Mann-Whitney *U* Test. Values within groups were compared with Wilcoxon signed rank test. Values are presented as median (interquartile range, total range)

LLL, volume of the left liver lobe in millilitres; *TLV*, total liver volume in millilitres; *VFA*, visceral fat area at L3–L4 level in square centimetres; *SMA*, skeletal muscle area at L3–L4 level in square centimetres

*$p < 0.05$ vs. T1; **$p < 0.01$ vs. T1; ***$p < 0.001$ vs. T1

omega-3 group BMI 43 (6) vs. 31 (6), $p = 0.000$. Elevated fasting glucose was present in the LCD group in 8.3 vs. 10.3% in the omega-3 group ($p = 1.000$). Elevated blood pressure was present in the LCD group in 16.7% vs. 21.1% in the omega-3 group ($p = 1.000$). Dyslipidaemia was present in the LCD group in 20.8% vs. 13.8% in the omega-3 group ($p = 0.715$).

Discussion

In this randomised controlled study in morbidly obese women, omega-3 supplementation of a 2000-kcal diet and a LCD of 800 kcal reduced LLL, TLV and VFA in morbidly obese women. The LLL and TLV reducing effects were significantly larger with the LCD. The significant loss of SMA in the LCD group was not seen with the omega-3 treatment as were the side effects and lower compliance. Although the omega-3 diet did not outperform the LCD, the significant reduction in LLL, TLV and VFA is remarkable especially in light of the higher caloric dietary load in the supplemented group.

Our results support the study of Ianelli et al. who supplemented 20 morbidly obese patients with oral omega-3 fatty acids for 4 weeks before LRYGP without any dietary restrictions, and measured the volume of the left liver lobe with ultrasound. Similar inclusion criteria were used but their study lacked a common practice control group. Compared to our results, they found a larger decrease of LLL with omega-3 supplementation (− 20% vs. − 4%) that was even higher than achieved with our LCD (− 11.3%).

However, MRI measurement of LLV is more accurate and using ultrasound may have resulted in an overestimation of the effect. In a study by Jaser et al., ultrasound proved to be unreliable in evaluating the size and consistency of the left lobe of the liver prior to LRYGBP [9]. Second, the content of the diet that was supplemented with omega-3 was not defined in the study of Ianelli et al. and intake was not followed up. Patients may have continued their calorie-restrictive diet augmenting the omega-3 effect. In the present study, an example of a normal healthy diet was provided to prevent calorie restriction on top of the omega-3 supplement. The results indicate that omega-3 supplementation without calorie restriction can reduce liver volume in obese women.

An important negative effect of the LCD in our study was the significant loss of skeletal muscle mass even after a short period of 2 weeks. The results of the present study confirm data from a recent study by Kim et al. who showed significant loss of skeletal muscle mass and strength after 12 weeks of calorie restriction in obese men [10]. In a review of Zibellini et al., the current literature also suggests a potential adverse effect of diet-induced weight loss on muscle strength. Loss of muscle mass may impede recuperation after surgery and our finding emphasises the risks of LCDs in these patients.

An interesting finding was the preservation of muscle mass in the omega-3-supplemented group despite similar weight loss compared to the LCD group. Adequate nutrition probably has played an important role. However, there is increasing evidence that omega-3 fatty acids may preserve muscle mass by influencing intrinsic anabolic/anti-catabolic properties, metabolic flexibility, insulin resistance and inflammation in muscle tissue [11]. For example, in a randomised trial by Smith et al., 8 weeks of oral omega-3 fatty acids increased muscle protein synthesis in older adults, another category of patients at risk of sarcopenia [12]. In addition, another study by the same authors showed that 6 months of oral omega-3 fatty acids increased muscle volume and strength in older adults [13]. In addition, Lalia et al. found increased mixed muscle and mitochondrial and sarcoplasmic protein synthesis rates after 16 weeks of oral omega-3 fatty acids [14]. Although the supplementation period of 4 weeks was shorter in the present study, these metabolic effects of omega-3 fatty acids may have played a role in muscle preservation.

The surgeons reported difficult access to the lesser sac in only 1 LCD patient and 3 omega-3 patients, which was not significantly different. Although the reduction in liver volume was significant in both groups, the actual absolute differences were quite small. This raises the question whether a dietary intervention is at all necessary in every patient to reduce liver volume. Perhaps, it is more cost effective to screen patients for large LLV which may help narrow the target group. While ultrasound is unreliable, MRI could be used as a screening

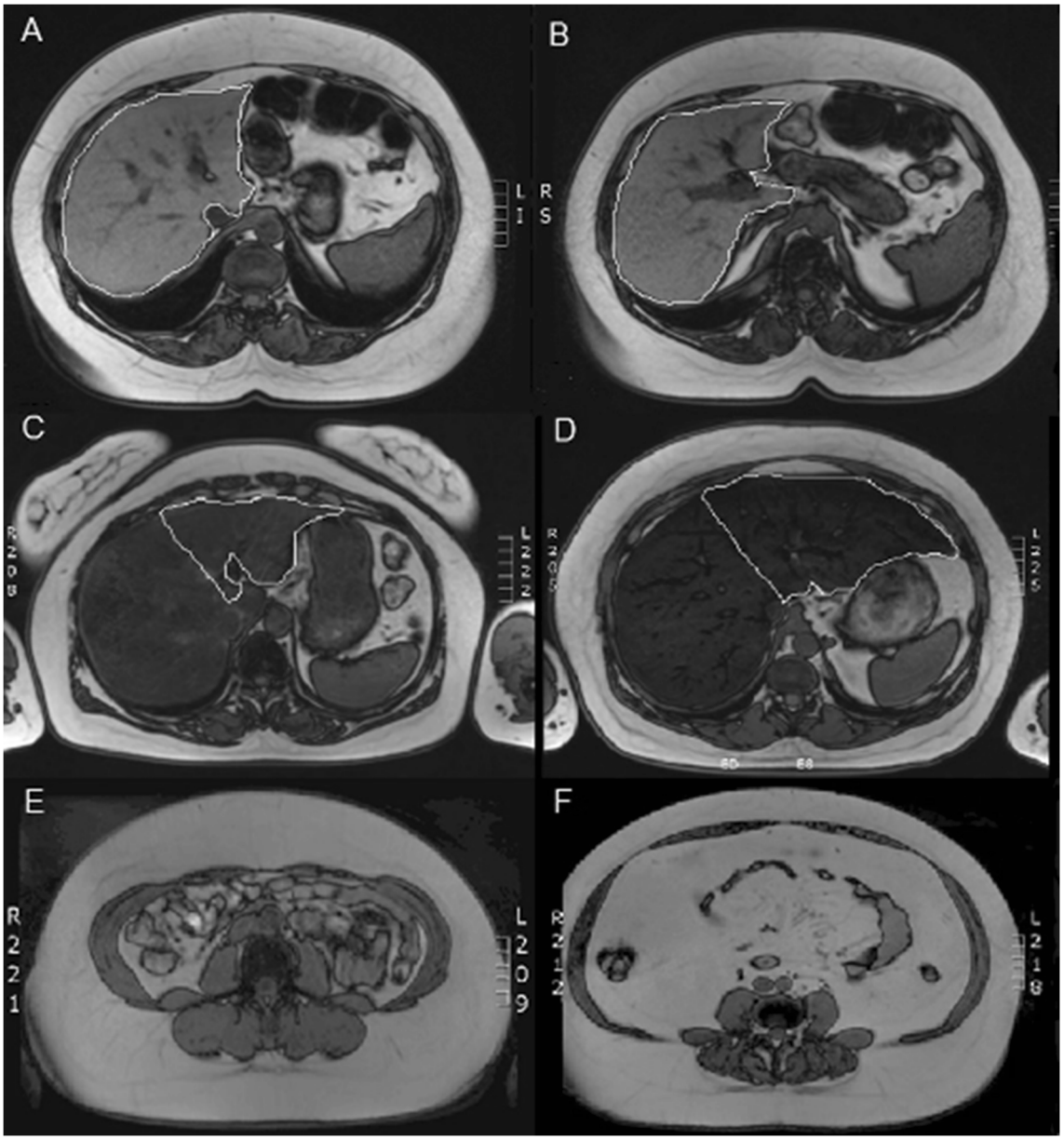

Fig. 2 Examples of MRI measurements. **a**, **b** Total liver volume before and after preoperative treatment. **c** Small left liver lobe. **d** Large left liver lobe. **e** Small visceral fat area. **f** Large visceral fat area

Table 3 Patient interview

	LCD ($n = 25$)	Omega-3 ($n = 29$)	p value
Bad taste	7 (28)	0 (0)	0.003
Hunger	17 (68)	5 (17)	0.000
Nausea/vomiting	6 (24)	1 (3.4)	0.041
Diarrhoea/loose stool	4 (16)	4 (13.8)	1.000
Constipation	7 (28)	1 (3.4)	0.019
Compliance difficulty	10 (40)	2 (6.9)	0.004
Non-compliance ≥ 3 times	9 (36)	2 (6.9)	0.008

Values in parentheses are percentages

tool. Besides the size of the liver, the rigidity that comes with steatosis is probably of similar importance and difficult to estimate preoperatively.

In this study, we found a decrease in VFA in both groups. This is in accordance with a study of Sato et al., where oral administration of EPA reduced abdominal visceral and epicardial adipose tissue [15]. While visceral obesity is associated with an increased risk of metabolic complications [16], the loss of visceral fat contributes to the improvement of the metabolic profile. In addition, this also facilitates the LRYGB while a large amount of visceral fat may prevent the mobilisation of the small intestine necessary to make the gastro-jejunal anastomosis.

Table 4 Surgeon interview

	LCD ($n = 26$)	Omega-3 ($n = 30$)	p value
Liver enlarged	8 (31)	11 (38)	0.642
Fatty liver	10 (39)	10 (33)	0.690
Difficult manipulation	1 (4)	3 (10)	0.615
Access to lesser sac difficulty	1 (4)	3 (10)	0.615

Values in parentheses are percentages

This study has several limitations that have to be taken into account. Only women were included in this study but omega-3 fatty acids may have different effects in men. Only a small proportion (7/56) of the patients were qualified as super obese (BMI > 50), a category of patients where the effects of omega-3 fatty acids may be more pronounced. The exclusion of patients that did not fit in the MRI provides a source for selection bias; however, with the currently used criteria, no candidates had to be excluded based on weight or waist circumference. Patients were interviewed about compliance but we did not confirm it with biochemical tests. The interviewer was not blind to treatment allocation, but bias was avoided as much as possible by asking the questions in a structured, uniform way. Last, with MRI, absolute liver volumes were estimated, but to estimate the chance of difficult access to the lesser sac, it is probably more accurate to look at liver volume in relation to total abdominal volume of the patient.

Conclusions

In conclusion, as part of a 2000-kcal diet, oral omega-3 supplementation is capable of reducing LLL and TLV but not to the extent achieved with a 800-kcal LCD diet. Compared to omega-3, the use of the LCD coincided with more side effects, worse compliance and significant loss of SMA that was not seen in the omega-3 group. Difficulty with surgical approach due to enlarged livers as reported by the surgeon was not different between the groups and a larger-sized study is needed to address this topic. Our results suggest that the preoperative use of omega-3 fatty acids in conjunction with a normal diet is a feasible alternative for a LCD to reduce liver volume and VFA with preservation of muscle mass. Screening imaging of liver volume in patients scheduled for LRYGB may be considered to select patients with very large livers that specifically need pretreatment to reduce liver volume. Further investigation of the effects in patients with a higher BMI, in men and in patients undergoing other kinds of surgery, is necessary.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval and Informed Consent 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. Informed consent was obtained from all individual participants included in the study.

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