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Original Article

Effects of sleeve gastrectomy and Roux-en-Y gastric bypass on non-alcoholic fatty liver disease in Iranians with morbid obesity

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A B S T R A C T

Background: Morbid obesity increases the risk of various diseases, including non-alcoholic fatty liver disease (NAFLD). Bariatric surgery is one of the most effective tools to achieve significant weight loss and reduce complications in morbidly obese people. The present study was conducted to assess the effects of bariatric surgery on NAFLD-related factors.
Methods: This quasi-experimental study was conducted among 40 patients with obesity who underwent sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) between July and November 2020. Biochemical factors and liver steatosis were evaluated by ultrasonography.
Results: The results revealed a significant decrease in alanine aminotransferase, triglyceride, and low-density lipoprotein levels in both groups. After RYGB, a significant decline was observed in aspartate aminotransferase, alkaline phosphatase, and total cholesterol (TC) levels. In contrast, after SG, high-density lipoprotein levels were considerably elevated. Ultrasonography results showed a significant reduction in steatosis following RYGB, but not SG. However, no significant differences were observed between the two groups, except in TC levels.
Conclusion: This study demonstrated that SG and RYGB had significant and beneficial short-term (6-month) effects on biochemical factors such as lipid profiles, liver enzymes, and blood glucose levels. While RYGB showed a slight advantage over SG in some parameters, the only statistically significant difference between groups was in the TC level. Furthermore, ultrasound findings revealed no statistically significant differences between SG and RYGB, suggesting that both procedures are effective at improving steatosis.

Keywords: Bariatric surgery; Lipids; Liver; Non-alcoholic fatty liver disease; Obesity, morbid

Introduction

With the constant increase in obesity worldwide,[1] the rates of associated complications such as type 2 diabetes mellitus, gallbladder disease, hypertension, cardiovascular disease, obstructive sleep apnea, and some types of cancer have dramatically escalated.[2,3] The obesity epidemic has also caused a rise in non-alcoholic fatty liver disease (NAFLD).[4] In most studies, the prevalence of NAFLD has been estimated to range from 25% to 45%, and it has increased along with obesity and diabetes.[5] NAFLD is characterized by a broad spectrum of liver damage including non-alcoholic fatty liver, non-alcoholic steatohepatitis, cirrhosis, and fibrosis, which may be accompanied by hepatocarcinoma and hepatic failure.[6]

Many factors have been hypothesized to cause NAFLD, but the exact cause is unknown. The two-hit hypothesis suggests that NAFLD results from the hepatocytic accumulation of triglycerides (TGs), which causes steatosis. Affected hepatocytes are more susceptible to the second hit caused by inflammatory cytokines, adipokines, mitochondrial dysfunction, and oxidative stress, which can lead to steatohepatitis and/or fibrosis. Nonetheless, it is essential to note that TGs do not directly cause liver damage; rather, they are assessed as a marker of exposure to potentially toxic free fatty acids.[7] NAFLD is characterized by insulin resistance and dyslipidemia. Obesity and central obesity are related to excess free fatty acid supply to the liver and consequent insulin resistance.[8] In people with obesity, chronic inflammation due to lipid accumulation also contributes to NAFLD development. B cells and other immune cells can release inflammatory cytokines and immunomodulatory mediators that can mediate hepatocyte

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necrosis, liver steatosis, and liver fibrosis in NAFLD.[9] Weight loss is essential for the improvement of NAFLD, as the current guidelines indicate that weight loss can decrease steatosis.[9,10]

As most cases of obesity are refractory to lifestyle modification and few truly effective pharmaceutical agents exist for treating obesity, particularly morbid obesity, bariatric surgery is the best alternative to help people lose weight.[11,12] Evidence has indicated that bariatric surgery can significantly improve or resolve comorbidities associated with obesity such as type 2 diabetes, hypertension, sleep apnea, and dyslipidemia.[13] Moreover, some studies have reported improvements in steatosis and steatohepatitis following bariatric surgery in NAFLD.[14–18] However, the efficacy of bariatric surgery in NAFLD has remained unclear. Therefore, the present study was designed to assess the effect of weight loss after bariatric surgical procedures on liver biochemical factors and sonography during a 6-month follow-up period.

Methods

Patients and study design

This quasi-experimental study was conducted among patients referred to the obesity center of the Qadir Mother and Child specialized hospital in Shiraz, Iran between June and November 2020. The participants included 40 obese patients (33 females and 7 males) with NAFLD who were candidates for sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) and were selected through non-randomized sampling. The patients were evaluated for bariatric surgery by a multidisciplinary committee that included a psychologist, a nutritionist, surgeons, and sports physicians. The inclusion criteria of the study were body mass index (BMI) $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with comorbidities, diagnosis of NAFLD, and at least 18 years of age. The exclusion criteria were alcohol consumption $\geq$ 20 g/day for females and $\geq$ 30 g/day for males, lactation, chronic hepatitis B or C virus infection, and taking of medications known to cause hepatic steatosis or liver damage. Patients who had previously undergone bariatric surgery were also excluded. After being informed of study objectives and confidentiality, the participants were required to sign written informed consent forms. The study was approved by the institutional ethics committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.245).

Outcomes

The primary outcome of the study was the change in the grade of NAFLD 6 months after surgery. The secondary outcomes were the impacts of bariatric surgery on body weight and biochemical parameters such as blood glucose level, lipid profile levels, and liver enzyme levels.

Study variables

At the beginning of the study, the patients' demographic characteristics (age, marital status, education level, occupation, medical history, eating habits, medications and supplements, and history of smoking and alcohol consumption) were collected. In addition, physical activity was assessed using the International Physical Activity Questionnaire at the beginning and end of the study. Clinical data including BMI, percentage total weight loss (%TWL), percentage excess weight loss (%EWL), and presence of comorbidities (hypertension and hypothyroidism) were analyzed preoperatively and 6 months after surgery. BMI was calculated as weight (kilograms) divided by the square of height (meters). Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or prior use of antihypertensive drugs. Biochemical parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), TG, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fasting blood sugar levels were measured in the laboratory of Qadir Hospital before and 6 months after surgery. Standard laboratory methods were used for all measurements. Levels of each liver enzyme were considered elevated or abnormal based on at least one measurement of the following: ALT level > 45 U/L in male and > 34 U/L in female patients; AST level > 35 U/L in male and > 31 U/L in female patients; ALP level > 129 U/L in male and > 104 U/L in female patients. Normal serum lipid levels were defined according to the National Cholesterol Education Program Adult Treatment Program III guidelines as follows: TG, < 150 mg/dL; TC, < 200 mg/dL; LDL, < 130 mg/dL; and HDL, > 40 mg/dL.

Surgical technique and selection

The bariatric procedures performed were SG and RYGB. All bariatric surgery was laparoscopic and was carried out by the same surgical team according to standard techniques.

Under general anesthesia, a standard five-port laparoscopic approach was used for surgery. Following a longitudinal resection from approximately 6 cm proximal to the pylorus to the angle of His with a linear stapler, SG was performed. To calibrate the remaining stomach, a 32-F bougie was inserted along the lesser curvature and reinforced with an omental pouch. The steps for RYGB were gastric pouch creation, biliopancreatic limb creation, jejunojejunostomy creation, and gastrojejunostomy creation.

Those who met the criteria for surgery were referred to an obesity clinic where they were evaluated by psychologists, cardiologists, endocrinologists, nutritionists, dietitians, and anesthesiologists. A specialized team at the hospital took a complete history of each patient, including physical activity patterns, current eating habits, and details of all previous attempts to lose weight. In addition to explaining the surgical technique, advantages, disadvantages, and complications, the surgeon also inquired about patient preferences and expectations. Accordingly, the type of surgery was chosen for each patient.

Ultrasonographic evaluation

NAFLD was assessed using a SonoAce R5 ultrasound device (Samsung) with a 3.5-MHz convex probe. One radiologist performed general abdominal ultrasonography at the same hospital. We diagnosed fatty liver with ultrasonography based on standard criteria, including liver and kidney echogenicity differences and the visibility of the intrahepatic vessel walls. Accordingly, fatty liver was classified as mild (grade I), moderate (grade II), or severe (grade III). Grade I was characterized by the smallest increase in liver echogenicity, with the liver appearing brighter than the kidney cortex and the intrahepatic vessel walls clearly visualizable. Hepatic echogenicity was moderately greater in grade II, and the echo line of the intrahepatic vessels was lost. Grade III involved a severe increase in the echogenicity of the liver and poor penetration of the posterior segment of the right lobe.[19,20]

Data analysis

The collected data were analyzed using IBM SPSS version 21

(IBM Corp.). The Kolmogorov-Smirnov test was used to determine the normality of the data. Then, the chi-square test was used to compare the demographic characteristics of the participants. Additionally, baseline data of the two groups were compared using the Mann-Whitney test. The Wilcoxon test was utilized to compare the mean changes in each group before and after surgery. Descriptive statistics were given as mean ± standard deviation, and P-values < 0.05 were considered to indicate statistical significance.

Results

Baseline characteristics of patients

Among the 40 patients (33 females and 7 males), 30 underwent RYGB and 10 underwent SG. No patient was excluded during the study. The mean age of the patients was 39.15 ± 12.24 years. Hypertension and hypothyroidism were detected in 25.0% and 22.5% of patients, respectively. The results revealed no significant differences between the two groups regarding the demographic characteristics and comorbidities (Table 1).

Obesity-associated comorbidities

The main obesity-related comorbidities in the present study were hypertension (found in 10 of the patients, or 25.0%), hypothyroidism (found in 9 patients [22.5%]), heartburn (8 patients [20.0%]), knee pain (15 patients [37.5%]), sleep apnea (2 patients [5.0%]), asthma (6 patients [15.0%]), and type 2 diabetes (1 patient [2.5%]) (Table 1).

Weight loss following SG and RYGB

The mean preoperative weight was 116.05 ± 23.52 kg in the SG group and 120.85 ± 19.11 kg in the RYGB group. The mean BMI had fallen from 43.48 ± 5.34 kg/m^2 to 32.77 ± 5.46 kg/m^2 (P = 0.005) and from 44.59 ± 6.33 kg/m^2 to 32.83 ± 5.88 kg/m^2 (P < 0.001) 6 months after SG and RYGB, respectively. The mean %EWL was 50.03% ± 27.68% after SG and 54.11% ± 19.09% after RYGB. Furthermore, the mean %TWL was 26.29% ± 17.48% after SG and 26.64% ± 8.62% after RYGB. After 6 months, no significant difference was observed between the two groups in %EWL or %TWL (Table 2).

Table 1 Comparison of Baseline Patient Characteristics

Variable	Sleeve gastrectomy (n = 10)	Roux-en-Y gastric bypass (n = 30)	P-value
Age (yr)	37.90 ± 14.20	39.57 ± 11.75	0.827
Sex			
Female	9 (90.0)	24 (80.0)	0.656
Male	1 (10.0)	6 (20.0)	
Weight (kg)	116.05 ± 23.52	120.85 ± 19.11	0.281
BMI (kg/m^2)	43.48 ± 5.34	44.59 ± 6.33	0.365
Hypertension	1 (10.0)	9 (30.0)	0.401
Hypothyroidism	1 (10.0)	8 (26.6)	0.404
Heartburn	4 (40.0)	4 (13.3)	0.089
Knee pain	5 (50.0)	10 (33.3)	0.457
Sleep apnea	1 (10.0)	1 (3.3)	0.442
Asthma	1 (10.0)	5 (16.6)	0.999
Type 2 diabetes	1 (10.0)	0 (0)	0.250
ALT (IU/L)	33.88 ± 21.58	34.40 ± 26.62	0.907
AST (IU/L)	25.00 ± 12.62	27.76 ± 14.46	0.377
ALP (IU/L)	168.70 ± 58.48	182.52 ± 55.07	0.465
TC (mg/dL)	183.44 ± 36.43	194.13 ± 29.51	0.677
TG (mg/dL)	195.11 ± 117.90	156.96 ± 60.94	0.680
LDL-C (mg/dL)	115.88 ± 31.69	121.93 ± 27.29	0.810
HDL-C (mg/dL)	39.66 ± 7.74	46.08 ± 11.72	0.144
FBS (mg/dL)	118.00 ± 64.74	97.25 ± 12.48	0.943
Physical activity (MET-min/week)	428.10 ± 259.4	453.17 ± 577.3	0.382
Fatty liver grading			
Grade I	5 (50.0)	14 (46.7)	0.999
Grade II	4 (40.0)	14 (46.7)	
Grade III	1 (10.0)	2 (6.7)	

Values are presented as mean ± standard deviation or number (%).
BMI, body mass index; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar; MET, metabolic equivalent of task.
P-values less than 0.05 were considered to indicate statistical significance.

Biochemical measurements following SG and RYGB

The results revealed a significant decline in ALT levels after both SG (P = 0.015) and RYGB (P = 0.001). AST and ALP levels decreased significantly only after RYGB, but the difference between the two groups was not statistically significant. In addition to changes in liver enzymes at the 6-month follow-up, significant reductions were observed in TG and LDL levels. Moreover, the patients who underwent RYGB experienced a significant decrease in TC (P < 0.001), with levels differing significantly from the SG patients ($P_{between\text{-}group}$ = 0.049). However, HDL increased significantly among the SG patients (P = 0.008). Furthermore, the fasting blood sugar level decreased significantly after both SG and RYGB, with no statistically significant differences between the two groups ($P_{between\text{-}group}$ = 0.430) (Table 2).

Table 2 Effects of SG and RYGB on Clinical and Biochemical Measurements

Variable	Surgery	Preoperative	Postoperative	*P*-value	*P*-value*
Weight (kg)	SG	116.05 ± 23.52	82.85 ± 13.86	0.005	0.435
	RYGB	120.85 ± 19.11	88.43 ± 16.23	< 0.001	
BMI (kg/m^2)	SG	43.48 ± 5.34	32.77 ± 5.46	0.005	0.901
	RYGB	44.59 ± 6.33	32.83 ± 5.88	< 0.001	
%EWL	SG	-	50.03 ± 27.68	-	0.595
	RYGB		54.11 ± 19.09		
%TWL	SG	-	26.29 ± 17.48	-	0.435
	RYGB		26.64 ± 8.62		
ALT (IU/L)	SG	33.88 ± 21.58	19.73 ± 8.58	0.015	0.839
	RYGB	34.40 ± 26.62	20.80 ± 9.92	0.001	
AST (IU/L)	SG	25.00 ± 12.62	18.70 ± 4.69	0.313	0.876
	RYGB	27.76 ± 14.46	20.46 ± 9.10	0.026	
ALP (IU/L)	SG	168.70 ± 58.48	143.66 ± 57.46	0.109	0.546
	RYGB	182.52 ± 55.07	170.72 ± 66.54	0.047	
TC (mg/dL)	SG	183.44 ± 36.43	181.22 ± 44.37	0.262	0.049
	RYGB	194.13 ± 29.51	153.20 ± 33.10	< 0.001	
TG (mg/dL)	SG	195.11 ± 117.90	121.90 ± 80.01	0.008	0.542
	RYGB	156.96 ± 60.94	102.26 ± 26.57	< 0.001	
LDL-C (mg/dL)	SG	115.88 ± 31.69	101.24 ± 31.72	0.011	0.192
	RYGB	121.93 ± 27.29	86.60 ± 18.91	< 0.001	
HDL-C (mg/dL)	SG	39.66 ± 7.74	48.90 ± 6.91	0.008	0.987
	RYGB	46.08 ± 11.72	49.41 ± 11.77	0.367	
FBS (mg/dL)	SG	118.00 ± 64.74	88.45 ± 8.50	0.041	0.430
	RYGB	97.25 ± 12.48	85.65 ± 8.14	0.001	

Values are presented as mean ± standard deviation.
SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; BMI, body mass index; EWL, excess weight loss; TWL, total weight loss; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar.
*Comparison of SG and RYGB. *P*-values less than 0.05 were considered to indicate statistical significance.

Table 3 Comparison of Liver Steatosis after RYGB and SG

Fatty liver grading	SG (n = 10)			RYGB (n = 30)			*P*-value*
	Preoperative	Postoperative	*P*-value	Preoperative	Postoperative	*P*-value	
Grade 0	0	6 (60.0)	0.193	0	15 (50.0)	0.017	0.880
Grade I	5 (50.0)	3 (30.0)		14 (46.7)	11 (36.6)		
Grade II	4 (40.0)	1 (10.0)		14 (46.7)	4 (13.3)		
Grade III	1 (10.0)	0		2 (6.7)	0		

Values are presented as number (%).
RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.
*Comparison of SG and RYGB. *P*-values less than 0.05 were considered to indicate statistical significance.

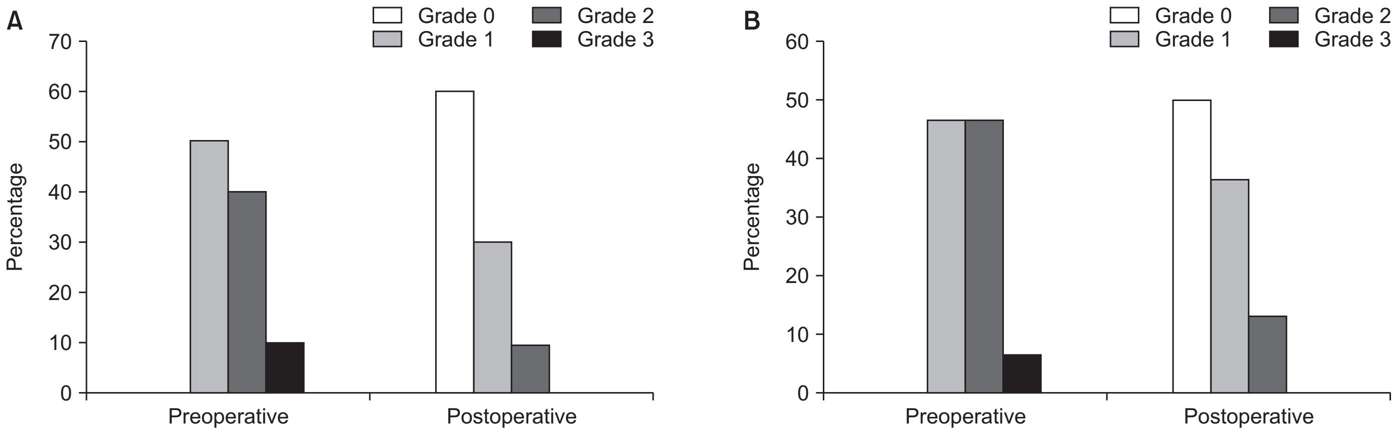

Fig. 1. Preoperative and postoperative grade of liver steatosis after sleeve gastrectomy (A) and Roux-en-Y gastric bypass (B).

Liver steatosis following SG and RYGB

Six months after surgery, 60.0% of the patients who had undergone SG and 50.0% of those treated with RYGB showed no steatosis of any grade. Moreover, grade 3 stenosis had completely disappeared from both study groups. However, a significant reduction was observed in steatosis among only the RYGB patients (P = 0.017). That said, no statistically significant difference was found between the two groups in this respect ($P_{\text{between-group}}$ = 0.880) (Table 3, Fig. 1).

Discussion

Obesity is one of the most critical risk factors for NAFLD. People with morbid obesity are particularly vulnerable to hepatic injury and progression to more dangerous stages of the disease, such as cirrhosis and liver failure. Due to the lack of definitive clinical treatment for this condition, weight loss has been considered the best way to deal with NAFLD in people with obesity.[4,6] Clinical treatments are not practical for long-term sustained weight loss, as nearly 95% of patients regain the lost weight within two years.[21] The most effective treatment for obesity and metabolic disorders is bariatric surgery, which can result in a weight loss of more than 55%.[22] Currently, RYGB and SG are the two most common weight-loss procedures globally.[23]

Our previous study showed that among patients with morbid obesity, more severe NAFLD was associated with higher weight and BMI; higher ALT, AST, TG, and fasting blood sugar levels; and lower HDL levels.[19] In the present study, as reported in other research, patients experienced significant reductions in %TWL, %EWL, and BMI after both SG and RYGB.[15,16,24] Furthermore, no significant differences were observed between the two groups in weight loss after 6 months, which aligned with the results of studies with longer follow-up periods.[25,26]

Similar to the current findings, the results of multiple studies have shown that bariatric surgical procedures improve hepatic aminotransferase levels.[15,18,27] However, the present study findings indicate that RYGB had advantages over SG in normalizing liver transaminases during the 6-month follow-up period. In contrast, Azulai et al[28] reported that relative to bypass surgery, SG was associated with a significant reduction in liver enzyme levels as well as a lower incidence of postoperative increase in ALT level. In a separate study of 500 individuals conducted by Guan et al,[27] the reduction of aminotransferase levels was significant in both SG and RYGB groups. Bariatric surgery has been found to reduce transaminase levels by reducing liver fat and inflammation as well as by improving insulin resistance following calorie restriction and appetite reduction.[29] Bariatric surgery also provides considerable metabolic benefits to the liver by reducing glucose production, improving insulin sensitivity, decreasing the very-low-density lipoprotein/TG secretion rate, and dramatically reducing the fat content of the liver.[30]

According to the results of this and previous studies,[16,31,32] the dyslipidemia status of patients improved after both SG and RYGB. However, RYGB was more effective than SG in lowering the TC level. In the same vein, Spivak et al[33] found that reductions in TC and LDL levels were significantly greater after RYGB compared to SG at 12 ± 4 months after surgery. Similarly, a number of studies[34–36] have demonstrated that SG improves the lipid profile mainly by reducing TGs and elevating HDL cholesterol, with little influence on LDL cholesterol. Additionally, Heffron et al[37] conducted a meta-analysis based on 178 studies and found that RYGB improves lipid profile more than SG.

Several studies have demonstrated that increased LDL and decreased TC after RYGB may be due to factors other than weight (such as neurohormonal factors).[33,38,39] Although the mechanisms contributing to the improvement of lipid profile after bariatric procedures remain unclear, some studies[38,40] have suggested that significant weight loss is primarily responsible for the improvement in the lipid profile following RYGB. However, the RYGB approach also reduces the preference for a high-fat diet and increases the content of fecal fat.[40]

Losing weight leads to improved insulin sensitivity and glucose metabolism, which may affect lipid-lipoprotein metabolism.[30] In line with previous findings, the current study showed an improvement in fasting blood glucose levels after bariatric surgery.[32,41,42] The normalization of blood glucose and insulin levels within a few days after surgery has not been well understood medically. However, in addition to improved glucose utilization and decreased insulin resistance, many factors—including changes in bile acid metabolism and nutrient sensing in the gastrointestinal tract as well as changes in the intestinal microbiome—have been identified as contributors. Increased secretion of glucagon-like peptide-1 after bariatric surgery may also play a role.[43]

Froylich et al[44] performed a cohort study of obese patients with NAFLD and found that both RYGB and SG effectively improved liver function and structure, but RYGB was more effective than SG in promoting NAFLD regression. A recent meta-analysis also indicated that bariatric surgery could resolve or halt the progress of liver fibrosis in 30% of patients, indicating that it was far more effective than any other treatment for non-alcoholic steatohepatitis. Those researchers also noted that RYGB had a greater effect than SG on the histological features of NAFLD.[45] According to ultrasound findings in the present study, no statistically meaningful differences were present between the two procedures (P = 0.880). The reduction in steatosis was statistically significant only after RYGB. However, both SG and RYGB appear effective in improving steatosis, and the lack of statistical significance in the SG results was likely due to the small samples of patients.

The strength of the present study was its comparison of two popular procedures and recognition of the differences between them, which may help surgeons determine the most appropriate procedure for obese patients with NAFLD. Nevertheless, the study had limitations, most notably the short follow-up period and the small number of patients in each group.

In conclusion, this study demonstrated the improvement of clinical and biochemical factors (lipid profiles, liver enzymes, and blood glucose levels) after both RYGB and SG. Improvement in these factors may indicate a protective role of bariatric surgery in chronic liver damage as well as the possible prevention of NAFLD progression to cirrhosis and fibrosis. Although RYGB showed a slight advantage over SG in some parameters, only the differences in TC level were statistically significant. However, further research with a larger sample size is needed to clarify the effects of these two types of surgery on NAFLD among patients with morbid obesity.

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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