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Bariatric Surgery Improves Histological Features of Nonalcoholic Fatty Liver Disease and Liver Fibrosis

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Abstract Nonalcoholic fatty liver disease (NAFLD) is prevalent in obese patients. We sought to determine the effects of bariatric surgery on the histological features of NAFLD. Two blinded pathologists graded liver biopsies done during bariatric procedures and subsequent operations in 160 patients using the Brunt classification. Data are mean±SD. Interval between biopsies was 31± 26 months. Initial biopsies demonstrated steatosis 77 %, lobular inflammation 39 %, and chronic portal inflammation 56 %. Steatohepatitis was present in 27 %. Grade 2–3 fibrosis was present in 27 %, and cirrhosis was present in one patient. On post-bariatric biopsy, steatosis resolved in 75 %, lobular inflammation resolved in 75 %, chronic portal inflammation resolved in 49 %, and steatohepatitis resolved in 90 %. Fibrosis of any grade resolved in 53 % and improved in another 3 % of patients. Grade 2 fibrosis resolved in 58 %, improved in 3 %, and did not worsen in 11 %. Bridging fibrosis resolved in 29 %, improved in 29 %, and did not worsen in 29 %. Bariatric surgery is associated with resolution of steatosis or steatohepatitis in the majority of patients. More importantly, grade 2 or 3 (bridging) fibrosis is resolved or improved in 60 % of patients. Bariatric surgery should be considered as a treatment of NAFLD in severely obese patients.

Keywords Roux-en-Y-gastric bypass · Liver injury · Cirrhosis · Liver biopsy · Lipotoxicity

Introduction

Nonalcoholic fatty liver disease (NAFLD) is probably the most common liver disease in Western countries and accounts for the majority of nonviral hepatitis-related liver transplantation.[1,2] NAFLD has a spectrum of histological features that include steatosis, steatohepatitis, fibrosis, or cirrhosis. It is estimated that 38 % of all patients have progression of fibrosis within 5 years after the diagnosis of NALFD is made.[3]

Risk factors for NALFD include diabetes, hyperlipidemia, and central obesity. The increasing prevalence of obesity has been accompanied by doubling of the prevalence of NAFLD in the last 20 years.[4]

Previously, we reported a high prevalence of NAFLD in patients undergoing bariatric surgery; liver biopsies done during bariatric procedures demonstrated steatosis (79 %), steatohepatitis (35 %), and unexpected fibrosis or cirrhosis in 9 %.[5]

Unlike alcoholic or viral hepatitis, the progression of obesity-induced liver disease may be halted, if not reversed by weight loss. Although bariatric surgery has been shown to decrease the presence of NAFLD in obese patients,[6–12] fibrosis and cirrhosis have long been felt to be progressive and irreversible.[13,14] Nonetheless, we observed that several patients who were diagnosed with fibrosis at the time of bariatric procedure had an uneventful long-term recovery, thereby suggesting that the progression of fibrosis may have been halted

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by weight loss. Based on our anecdotal observations, we hypothesized that bariatric surgery improves the histological features of NAFLD. In this study, we aim to investigate and describe the impact of surgical weight loss on the histological features of hepatic steatosis, steatohepatitis, fibrosis, and cirrhosis in severely obese patients who underwent bariatric surgery.

Materials and Methods

Routine liver biopsies were obtained during bariatric procedures to confirm the diagnosis and stage of NAFLD. A subset of patients who required subsequent abdominal operations from 1999 to 2013 for various indications (abdominal pain, bowel obstruction, hernia, etc.) underwent a concomitant liver biopsy for follow-up of diagnosis of NAFLD. All 181 consecutive patients who underwent bariatric surgery for obesity and a subsequent abdominal operation and in whom a liver biopsy was done during the two procedures were included in the study.

Twenty-one patients were excluded due to the following: missing slides or identifying information (12 patients), revisional procedures (7 patients), or insufficient specimens (2 patients). The 160 pairs of liver biopsies were examined by two independent liver pathologists. The relationship between improvements in histological features and clinical characteristics was assessed using retrospectively collected data including demographics and weight loss.

Patient Characteristics

Patients were referred for bariatric surgery to treat obesity and its associated comorbidities. Preoperative evaluations by an interdisciplinary team included history and physical examination, nutritional and psychiatric evaluation, and specialty consultations when indicated. Alcohol consumption or active hepatitis B or C infection was determined using a standard medical history questionnaire, nursing notes, or anesthesiologist preoperative visit.

Patients were excluded from the study if they had history of alcoholism (>60 g/day of alcohol), had evidence of autoimmune hepatitis, chronic hepatitis B or C virus, HIV, hemochromatosis, alpha 1 anti-trypsin deficiency, or Wilson disease. Patients whose liver biopsies showed evidence of cirrhosis were further assessed and tested for viral hepatitis markers.

Bariatric Operations

Operations were completed by either a laparoscopic approach or open. The bariatric procedures included Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding but not sleeve gastrectomy. Liver biopsies were obtained intraoperatively using a Tru-Cut biopsy device (Bard Max-Core, Covington, GA) before the liver was compressed and retracted. The Tru-Cut device was advanced, under direct visualization, into the parenchyma of the right lobe of the liver; multiple passes were done as needed to obtain an adequate tissue sample. The post-bariatric liver biopsies were performed in the course of subsequent abdominal operations from 1999 to 2013.

Histology

Slides were cut from formalin-fixed, paraffin-embedded tissue blocks and stained with hematoxylin and eosin (H&E) as well as Masson trichrome. The biopsies were evaluated by two experienced and independent pathologists. The pathologists were blinded to all patient information and dates of biopsies. The Brunt classification system was used to grade liver biopsies for the presence and severity of steatosis, inflammation, and fibrosis.[15–17]

Specifically, steatosis was graded on a scale from 0 to 3 according to the amount of fat that was present throughout the lobules: Grade 0 indicates <5 %, grade 1=5–33 %, grade 2=>33–66 %, and grade 3>66 %.

Lobular inflammation was graded on the number of clusters of inflammatory cells using a scale of 0–3: Grade 0 indicates no foci, grade 1 indicates <2 foci per ×200 field, grade 2 indicates 2–4 foci per ×200 field, and grade 3 indicates >4 foci per ×200 field. Chronic portal inflammation was graded on a scale of 0–2: Grade 0 indicates none, grade 1 indicates mild, and grade 2 indicates moderate. Steatohepatitis score is a composite of steatosis, hepatocyte ballooning, lobular inflammation, and chronic portal inflammation.

Fibrosis was graded on a scale of 0–4: Grade 0 shows no fibrosis, grade 1 indicates either centrilobular or sinusoidal fibrosis, grade 2 indicates both periportal and sinusoidal fibrosis, grade 3 indicates bridging fibrosis, and grade 4 indicates cirrhosis. In cases where there were incongruent readings by the two pathologists, the higher of the two scores was used for the purpose of this study.

Changes in Liver Histology on Follow-Up Biopsy

For the purpose of this study, we considered each of the histological features (steatosis, lobular inflammation, chronic portal inflammation, hepatocyte ballooning, steatohepatitis, or fibrosis) as "resolved" if the post-bariatric biopsy grade score became zero or "improved" if the post-bariatric biopsy score is less than the pre-bariatric score but greater than zero. We considered histological findings as "same" if it was equal to the pre-bariatric grade score. Histological features were considered "worse" on post-bariatric biopsy if the grade score was higher than the pre-bariatric grade score.

Statistical Analysis

Quantitative data are reported as mean±SD (standard deviation). Categorical variables are represented as absolute values and/or percentages. A paired Student's *t* test was used for within-group comparisons (pre-bariatric vs. post-bariatric liver biopsy). An extension of the McNemar test was used to evaluate differences in NAFLD scoring. Comparisons between groups were performed using the unpaired *t* test and the chi-square test for categorical variables. Bivariate analysis was performed to assess relationships between variables, multiple regression analysis was used to assess independent predictors of improvement or worsening in NAFLD scoring, and any significant relationships were described using odds ratios with 95 % confidence intervals. All statistical tests were two-tailed; *p* values less than 0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 160 patients (women 84 % and men 16 %) underwent bariatric surgery from 1998 to 2013. Age was 47 ±12 years (range 19–72) at the time of the index bariatric operation. Mean preoperative weight was 328±83 lbs (range: 217 to 614), corresponding to a BMI of 52±10 kg/m^2 (range 36 to 91). Patients with a diagnosis of type 2 diabetes were taking oral anti-hyperglycemic medications or insulin prescribed by their primary care physician or endocrinologist and had normal or elevated values of hemoglobin A1c. Patients with a diagnosis of hypertension were taking oral antihypertensive medications prescribed by their primary care physician or cardiologist and had well-controlled or fairly well-controlled blood pressures. Patients with a diagnosis of obstructive sleep apnea had undergone a sleep study and were found to have mild to severe obstructive sleep apnea and required continuous positive airway pressure (CPAP) for treatment. None of the patients consumed more than 30 g of alcohol daily. All of the patients either were never tobacco users or had ceased all tobacco use for at least 3 months at the time of surgical intervention. Table 1 summarizes the most common preoperative obesity comorbidities in our cohort.

The index bariatric operations consisted of laparoscopic or open Roux-en-Y gastric bypass (79 %), laparoscopic or open "long-limb" Roux-en-Y gastric bypass (13 %), and laparoscopic adjustable gastric banding (8 %). Roux-en-Y gastric bypass was done with a 15–30-cc gastric pouch, a stapled gastrojejunostomy in the cardia with a 25-mm circular stapler, a 40-cm biliopancreatic limb, and a 100–150 cm Roux limb with an antecolic, antegastric reconstruction. Similar technique was employed for the long-limb Roux-en-Y gastric bypass; the jejunoileostomy was done at 100 cm proximal to the ileocecal valve. Gastric banding was done using the pars flaccida technique.

Table 1 Clinical characteristics of 160 patients who underwent bariatric surgery

		Range
Age (years)	47±12	19 to 72
Women	83 %	
Pre-op weight (lb)	328±83	217 to 614
BMI (kg/m^2)	52±10	36 to 91
Type 2 diabetes	47 %	
Hypertension	59 %	
Obstructive sleep apnea	54 %	
History of alcohol use (>30 g/day)	8 %	
History of tobacco use	15 %	

The follow-up post-bariatric biopsies were done 31± 26 months after the index bariatric operation (median 20 months; range 1–111 months). The indications for these operations included repair of ventral incisional hernia (56 %), lysis of adhesions (15 %), repair of internal hernia and small bowel obstruction (14 %), malnutrition or refractory marginal ulcer (6 %), diagnostic for cancer (2 %), band erosion or slip (2 %), and perforated gastric ulcer (1 %). At the time of the follow-up post-bariatric liver biopsy, weight was 206±59 lbs, corresponding to a BMI of 33±8 kg/m^2. The average weight loss was 122± 61 lbs, which is an excess body weight loss of 62±22 %.

Liver Histology

Findings on the liver biopsy done at the index bariatric operation were as follows: steatosis 77 %, lobular inflammation 39 %, and chronic portal inflammation 56 %. Steatohepatitis was present in 27 % of patients. Fibrosis of any grade was present in 65 % of the patients; specifically, grade 2–3 fibrosis was present in 27 %. Cirrhosis was present in one patient.

Improvement of Histological Features

Representative photomicrographs of liver histology are shown in Fig. 1. The biopsy was obtained from the same three patients at the index bariatric operation and, subsequently, post-bariatric. The post-bariatric biopsy shows improvement of steatosis, inflammatory infiltrates, and fibrosis.

Improvement of Steatosis

Overall, steatosis was found in 33 (21 %) post-bariatric biopsies compared to 123 (77 %) pre-bariatric biopsies ($p<0.0001$). Grade by grade changes of steatosis after bariatric surgery are shown in Table 2; overall, steatosis resolved or

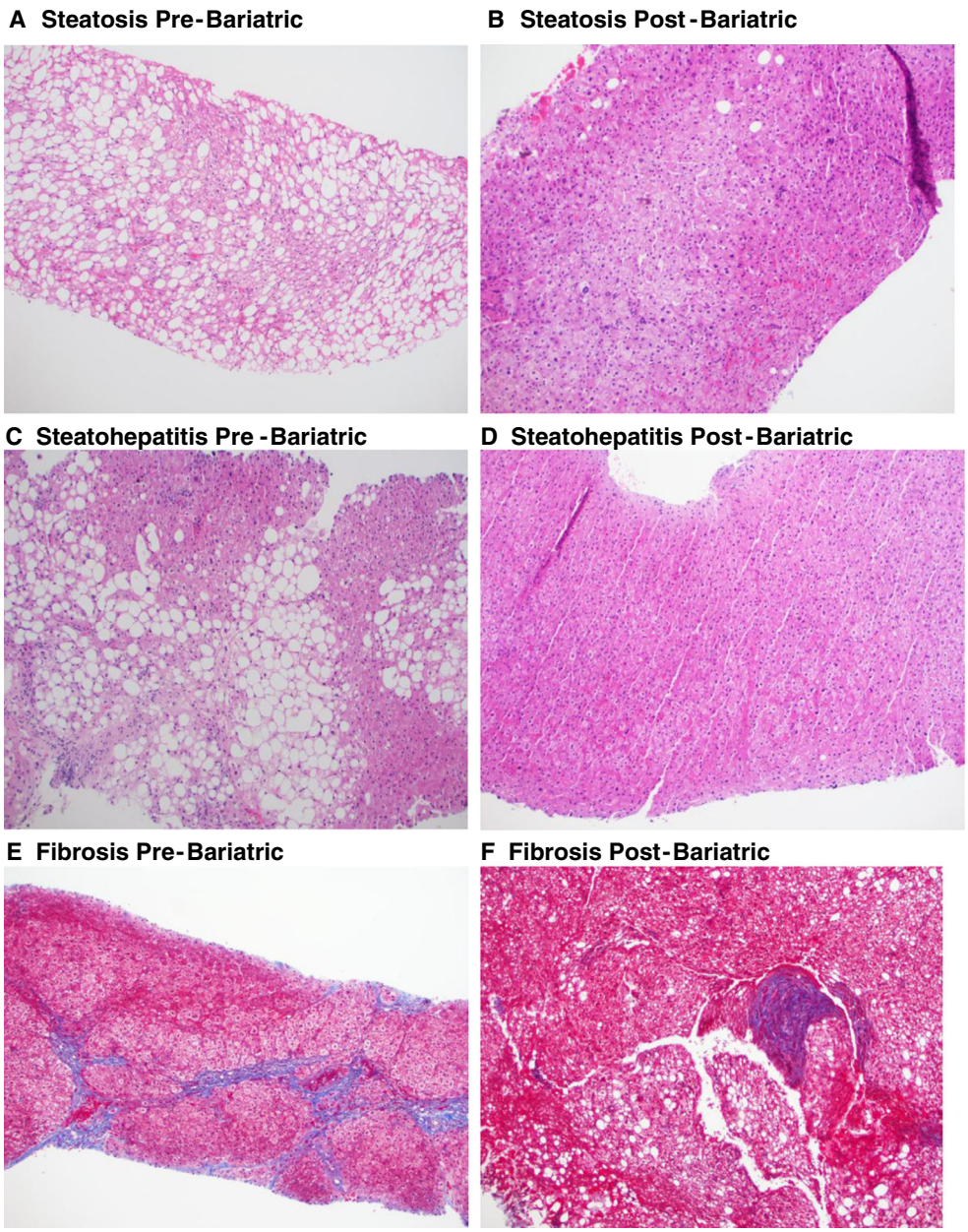

Fig. 1 Representative photomicrographs liver biopsies (H&E) done at the index bariatric procedure and post-bariatric biopsies. **a** Severe steatosis and fat deposition (microvesicular and macrovesicular) that resolved on the post-bariatric biopsy (**b**) from the same patient. Similarly features of steatohepatitis (**c**) improved on the post-bariatric biopsy (**d**). **e** Abundant fibrous tissue as seen with Mason trichrome that resolved in the post-bariatric biopsy (**f**)

improved in 75 and 11 % of patients, respectively. In eight patients (6 %), steatosis was graded worse on the post-bariatric biopsy.

Patients with grade 1 steatosis more commonly resolved steatosis on post-bariatric biopsy compared to grade 2 or 3 (odds ratio (OR) 2.6 [95 % confidence interval (CI) 1.1 to 6.2, p=0.03]). Only three patients (3/37) developed steatosis de novo after bariatric surgery.

Improvement of Features of Inflammation and Steatohepatitis

The number of patients with steatohepatitis decreased from 42 (26 %) to 5 (3 %) after bariatric surgery (p<0.0001). The majority of patients diagnosed with steatohepatitis were scored as grade 1 or 2 at the time of bariatric operation. Steatohepatitis resolved or improved in 93 % of patients.

Table 2 Improvement in steatosis in 160 patients after bariatric surgery

Pre-Bariatric	Post-bariatric			
	Resolved	Improved	Same	Worse
Grade 3 (n=25)	14 (56 %)	9 (36 %)	2 (8 %)	n/a
Grade 2 (n=37)	27 (73 %)	5 (14 %)	2 (5 %)	2 (5 %)
Grade 1 (n=61)	51 (84 %)	n/a	7 (11 %)	3 (5 %)
No steatosis (n=37)	n/a	n/a	34 (92 %)	3 (8 %)
Total (n=160)	92 (58 %)	14 (9 %)	45 (28 %)	8 (5 %)

Specifically, the number of patients with lobular inflammation decreased from 60 (39 %) to 26 (17 %) after bariatric surgery ($p<0.0001$). Lobular inflammation resolved or improved in 75 and 5 % of patients, respectively.

The number of patients with chronic portal inflammation decreased from 87 (56 %) to 57 (38 %) after bariatric surgery ($p<0.001$). Chronic portal inflammation resolved or improved in 49 and 16 % of patients, respectively.

Grade by grade changes for patients with features of inflammation and steatohepatitis after bariatric surgery are shown in Table 3. More commonly, patients who had grade 1 steatohepatitis had resolution of the inflammatory features after bariatric surgery (OR 48 [95 % CI 5.1 to 452, $p=0.0007$]). Only three patients (3/114) developed steatohepatitis de novo after bariatric surgery.

Chronic portal inflammation worsened in 9 patients (10 %) after bariatric surgery and developed de-novo in 18 patients (27 %). There were no instances of worsening lobular inflammation in the 60 patients who had this finding at the time of the bariatric operation. However, 15 patients developed lobular inflammation after surgery (16 %).

Improvement in Liver Fibrosis

Overall, the number of patients with fibrosis on liver biopsy decreased from 102 (65 %) to 58 (37 %) after bariatric surgery ($p<0.0001$). The majority of patients with fibrosis were grade 1 or 2 on the biopsy done at the time of bariatric operation; fibrosis resolved or improved in 53 and 3 % of patients, respectively.

Specifically, the number of patients with grade 1 fibrosis decreased from 58 (37 %) to 32 (20 %) after bariatric surgery. Grade 2 fibrosis decreased from 36 (23 %) to 14 (9 %) after bariatric surgery. Of the patients with grade 2 fibrosis, 21 (58 %) resolved, 1 (3 %) improved, and 4 (11 %) remained the same.

Of the seven patients with grade 3 (bridging) fibrosis, histological features of fibrosis resolved in two (29 %), improved in two (29 %), and remained the same in two (29 %) after bariatric surgery. Grade by grade changes in fibrosis are shown in Table 4.

Cirrhosis persisted in one patient. Cirrhosis was found on the post-bariatric biopsy in one patient who had grade 3 fibrosis at the time of the bariatric operation.

Of the 58 patients with grade 1 fibrosis on initial biopsy, progression of fibrosis to a higher grade was seen in 7 patients (12 %). An additional five patients (14 %) with grade 2 fibrosis progressed to grade 3 on the post-bariatric biopsy. There were 56 patients without fibrosis on initial biopsy, and of these, fibrosis developed de novo in 12 patients after bariatric surgery (21 %).

Factors Associated with Improvement or Worsening of Liver Histology

Bivariate analysis did not show significant associations between improvement in any individual aspect of liver histology (steatosis, steatohepatitis, or fibrosis) and any of the independent variables of age, gender, BMI, or weight loss. We did not test the associations between improvements in liver histology with the type of bariatric procedure since the majority of procedures were gastric bypass. Table 5 summarizes the weight loss and interval between biopsies for patients with changes in liver histology.

Because some of the liver biopsies were done before the nadir of weight loss and as early as 1 month post-operatively,

Table 3 Improvement in steatohepatitis and inflammation in 160 patients after bariatric surgery

Pre-bariatric	Post-bariatric				
		Resolved	Improved	Same	Worse
Lobular inflammation	Grade 2 ($n=10$)	6 (60 %)	3 (30 %)	0	n/a
	Grade 1 ($n=50$)	39 (78 %)	0	8 (16 %)	0
	None ($n=95$)	n/a	n/a	78 (82 %)	15 (16 %)
	Total ($n=155$)	45 (29 %)	3 (2 %)	86 (55 %)	15 (10 %)
Portal inflammation	Grade 2 ($n=17$)	9 (53 %)	5 (29 %)	3 (18 %)	n/a
	Grade 1 ($n=70$)	34 (49 %)	9 (13 %)	22 (31 %)	9 (13 %)
	None ($n=67$)	n/a	n/a	47 (70 %)	18 (27 %)
	Total ($n=155$)	43 (28 %)	14 (9 %)	72 (46 %)	27 (17 %)
Steatohepatitis	Grade 3 ($n=1$)	0	1 (100 %)	0	n/a
	Grade 2 ($n=8$)	6 (75 %)	0	1 (13 %)	0
	Grade 1 ($n=33$)	32 (97 %)	n/a	0	0
	None ($n=114$)	n/a	n/a	111 (97 %)	3 (3 %)
	Total ($n=156$)	38 (24 %)	1 (1 %)	112 (72 %)	3 (2 %)

Table 4 Improvement in fibrosis in 158 patients after bariatric surgery

Pre-Bariatric	Post-bariatric			
	Resolved	Improved	Same	Worse
Grade 4 (n=1)	0	0	1 (100 %)	n/a
Grade 3 (n=7)	2 (29 %)	2 (29 %)	2 (29 %)	1 (14 %)
Grade 2 (n=36)	21 (58 %)	1 (3 %)	4 (11 %)	5 (14 %)
Grade 1 (n=58)	31 (53 %)	N/a	18 (31 %)	7 (12 %)
No fibrosis (n=56)	n/a	n/a	43 (77 %)	12 (21 %)
Total (n=158)	54 (34 %)	3 (2 %)	68 (43 %)	25 (16 %)

Grade 3 is bridging fibrosis; grade 4 is cirrhosis. Two patients did not have adequate tissue samples for the reviewing pathologist to make a final recommendation

we tested the association between worsening of histological features and time to post-operative biopsy. In doing this subgroup analysis, we assumed that the nadir of weight loss is at 1 year post-operatively; the group of 8/28 patients who had liver biopsy within the first post-operative year showed worsening fibrosis compared to 11/103 patients whose biopsies were obtained more than 1 year post-operatively (OR 3.4 [95 % CI 1.2 to 9.6], p=0.012).

We also tested the association of worsening inflammatory changes such as an increase in the grade of chronic portal inflammation with the time interval between the two biopsies. Bivariate analysis revealed that the time interval between biopsies was shorter in patients who had chronic portal inflammation developing into a higher grade compared to all other patients (1.7 vs 2.8 years, p=0.004).

Additionally, we tested the likelihood of progression of histological findings based on the stage at the index bariatric operation using bivariate analysis. Steatosis in the initial biopsy was associated with worsening fibrosis (OR 8.8 [95 % CI 1.2 to 67.8, p=0.036]); a weaker association was found between steatohepatitis in the initial biopsy and worsening fibrosis after bariatric surgery (OR 2.8 [95 % CI 1.1 to 6.9, p=0.026]). Multiple regression analysis shows that the steatosis (grades 1–3) on the initial biopsy was an independent risk factor for worsening fibrosis on post-bariatric biopsy (r=0.32, p=0.0001) (OR 8.7 [95 % CI 1.1 to 66.9, p=0.0371]).

Discussion

In this study of 160 patients, we present objective evidence of resolution and significant improvement in the histological features of NAFLD after bariatric surgery. Steatosis resolved in three quarters of patients, steatohepatitis resolved in 90 % of patients, and fibrosis resolved in over half of patients.

NAFLD has a spectrum of histological manifestations, namely steatosis, inflammation and fibrosis, and tissue remodeling. The incidence of steatosis, steatohepatitis, and fibrosis in our cohort is consistent with our previously reported data[5] and data reported by others.[18] In patients undergoing bariatric surgery, the prevalence of NAFLD is 84–96 %, NASH is 25–55 %, any grade of fibrosis is 34–47 %, and bridging fibrosis or cirrhosis is reported in 2–12 %.[5,18]

Several studies support the hypothesis that NAFLD can progress to fibrosis; in an observational study of 52 overweight individuals, follow-up liver biopsy at 3 years demonstrated progression of fibrosis in 14 (27 %) patients; in another 13 (25 %) patients, fibrosis regressed. In the remaining 25 patients (48 %), no change was noted. Furthermore, reduction in body mass index and waist circumference was independently associated with nonprogression of disease activity and fibrosis.[21] Similarly, Adams et al.[22] described changes in histological features of NAFLD in 103 patients who had follow-up biopsies done 0.7–21 years after the histological diagnosis was confirmed. Fibrosis progressed in 37 %, remained unchanged in 34 %, and regressed/improved in 29 %. Patients with obesity and diabetes were identified as being at increased risk for progression of disease.

Risk factors for developing NAFLD are obesity, diabetes, and hyperlipidemia; although many studies assess the longitudinal progression of NAFLD to steatohepatitis or fibrosis in small cohort, very few of these patients meet the weight classification of class III obesity (BMI >40 kg/m^2), and therefore, the risk and rate of progression of NALFD in bariatric patients remain unknown. Nonetheless, surgically induced weight loss eliminates these risk factors for NALFD in the majority of patients and therefore reduces the otherwise perceived high likelihood of disease progression. The impact of bariatric surgery on the histology of NAFLD has been reported by others and has been linked to improvements in biochemical parameters and insulin resistance.[7,14]

Table 5 Weight loss and interval between biopsies for patients with changes in liver histology

Change in histology	Weight loss (%EBWL)	Interval between biopsies (days)
Improvement in steatosis (n=106)	62±22 (range 3.4 to 105)	967±819 (range 24 to 3,381)
Worsening in steatosis (n=8)	64±31 (range 13 to 109)	979±847 (range 69 to 2,513)
Improvement in steatohepatitis (n=39)	62±23 (range 10 to 98)	979±912 (range 140 to 3,381)
Worsening in steatohepatitis (n=3)	41±35 (range 13 to 80)	372±544 (range 46 to 1,000)
Improvement in fibrosis (n=62)	63±22 (range 3 to 109)	1013±846 (range 37 to 3,310)
Worsening in fibrosis (n=25)	60±28 (range 6 to 98)	840±872 (range 46 to 3,157)

The two-hit model is proposed to describe the progression from steatosis to steatohepatitis.[23,24] The "first hit" is deposition of excess fat in the liver owing to peripheral insulin resistance, which then leads to increased lipolysis and overabundance of free fatty acids. The "second hit" is characterized by hepatocellular injury and fibrosis secondary to proinflammatory mediators, oxidative stress, and mitochondrial dysfunction. We previously reported that gastric bypass in a rat model of diet-induced obesity improves insulin resistance, diminishes intrahepatic fat content, reduces oxidative stress, and improves mitochondrial dysfunction as well as reverses histological features of NALFD.[25–27] We are proposing that improvement in NAFLD after bariatric surgery in humans follows the same mechanistic pathways.

Our findings of the impact of bariatric surgery on liver histology are consistent with other studies; however, in a large study, fibrosis was found to slightly increase in biopsies done at 1 and after 5 years after bariatric surgery.[14] There are several possibilities that may explain the difference in fibrosis progression; in the study by Mathurin et al., the patients underwent Roux-en-Y gastric bypass, gastric banding, or bilio-intestinal bypass. The weight loss trajectories of the gastric banding and gastric bypass as well as the degree of weight loss are different and therefore may impact histological changes. Bilio-intestinal bypass has a prominent malabsorptive component that may worsen liver function and histology. Additionally, the post-bariatric follow-up biopsies in our cohort are done up to 12 years after the index bariatric operation.

The primary treatment of NAFLD in overweight or obese persons is weight loss and lifestyle modification. Modest weight loss (5 % of body weight) via nonoperative treatment improves histological features of NASH and resolves steatohepatitis in 67 % of patients on repeat liver biopsy.[19,20] In a randomized controlled study,[19] lifestyle modification improved the NAFLD Activity Score (NAS) compared to controls that did not loose weight; because of the differences in histological criteria, the findings of this study are not directly comparable to ours. While modest weight loss may lead to improvement of the NAS in patients with class I or II obesity, it is unknown whether a similar amount of weight loss will be helpful in patients with more severe obesity.

In another study of 15 patients with an average BMI of 34 at initial biopsy, a follow-up liver biopsy 12 months after intensive nutritional counseling found that 3/15 patients had worse fibrosis, 3/15 patients had improved fibrosis, and the remaining 9/15 did not change. Although the Brunt criteria were used in this study, the small sample size makes it difficult to draw conclusions about the effect of modest weight loss on changes in fibrosis.

Our study has several limitations related to the retrospective nature of the study and that the subsequent liver biopsies were not planned a priori, therefore it is unknown whether these patients were also receiving medications or other therapies that may have improved or worsened their liver histology. Another limitation is the lack of biochemical markers; we previously reported that abnormalities in parenchymal liver enzymes were not correlated with severity of histological findings.[5] Finally, the lack of standardization of timing for the second liver biopsy makes it challenging to outline the natural history of NAFLD after bariatric surgery with precision. Notwithstanding, we are reporting objective data that surgically induced weight loss improves the histological features of NAFLD. The ability to interrupt the progressive nature of NAFLD and liver fibrosis cannot be overemphasized.

In conclusion, we are presenting histological evidence of significant improvement in NAFLD after weight loss associated with bariatric surgery. The reversal of liver disease was universal across the spectrum of NAFLD and more importantly in the early stages of fibrosis. Our results provide compelling evidence that surgically induced weight loss should be considered the primary treatment of choice for patients with NAFLD and severe obesity.

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Discussant

Dr. Guilherme M. R Campos (Madison, WI):

The paper is an important contribution as it evaluated one of the larger cohorts of patients with paired liver biopsies at bariatric surgery and after significant weight loss as to study changes in liver histology for established markers of NAFLD. An important concept associated to the study is that individuals with predisposition to preferential accumulation of fat in the liver, in excess of deposits in the subcutaneous tissue or in other viscera are at higher risk for liver related diseases and other metabolic consequences. In other words, abnormal deposit of fat in the liver and the metabolic syndrome comes hand in hand, and bariatric surgery promotes loss of liver fat and improvements in liver histology and in the metabolic syndrome. This study documents the significant impact of surgically induced weight loss on specific NAFLD markers including improvement of liver fibrosis in 56 % of patients. It is important to underscore that the magnitude of histological improvements observed in this study is far greater than the observed with maximal nonoperative therapy and that till about 10 years ago liver fibrosis was considered, by most, to be an irreversible finding.

My questions to the authors are: 1. Were you able to identify any patient, surgical technique, the degree of weight loss or any other factor that correlated with improvement or worsening in the histologic markers of NAFLD and NASH?, 2. Because different bariatric surgical techniques provide for different weight loss outcomes and have different mechanisms that are independent of weight loss, some with a direct impact in liver physiology, should presence and severity of NAFLD, NASH or cirrhosis play a role in choosing a specific procedure or no procedure at all? and 3. Should a liver biopsy be considered a standard part of bariatric surgical procedures?

Closing Discussant

Dr. Taitano:

Thank you, Dr. Campos, for your comments and questions. There was no correlation between weight loss and improvement or worsening of histologic features. Patients who started at a higher BMI had an increased prevalence of steatosis and a higher frequency of grade 3 steatosis, but the degree of weight loss did not correlate with improvement or worsening of histologic features, and in particular it did not predict improvement or worsening of fibrosis. Using bivariate analysis, the only factors that were associated with worsening fibrosis were the presence of steatosis or steatohepatitis on initial biopsy.

Regarding different operations, the majority of patients in our study had a laparoscopic gastric bypass as their index operation and the small numbers of other operations such as gastric sleeve or banding do not allow for a valid comparison between operations. Despite this, we recommend weight loss surgery in general, and in particular, roux-en-y gastric bypass as a safe and effective treatment option for patients with fatty liver disease and severe obesity.

The findings on our earlier work of 660 liver biopsies done at the time of bariatric surgery suggest that although preoperative evaluation including clinical, radiology, and laboratory biomarkers are highly predictive of the presence of NAFLD, there is no current test available that predicts the presence of steatohepatitis or fibrosis with good sensitivity. We found a higher incidence of steatohepatitis and fibrosis when we performed routine liver biopsy compared to when we performed selective liver biopsy. Because of these findings, we have adopted routine liver biopsy for all our patients undergoing bariatric surgery, and we agree that it is the gold standard for the diagnosis of NASH and liver fibrosis.