Implication of Bariatric Surgery on NAFLD in Obese Patients

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ABSTRACT

Background: *Bariatric surgery results in favorable loss of excess weight, changes in co-morbidities and improvement in quality of life. In patients with non-alcoholic liver disease, liver histology taken before or during surgery reveals several histological abnormalities. In a prospective study of patients previously submitted to bariatric surgery, we determined the changes in liver histology late after the surgery.* ***Methods:*** *These 36 patients (11 males, 25 females) had two liver biopsies, the first at the time of laparoscopic sleeve gastrectomy (14 patients) and Laparoscopic OAGB (22 patients),and the second after weight loss. Second biopsies were obtained from two groups: those requiring a subsequent laparoscopic procedure (n = 19) and those who accept for percutaneos biopsy (n = 17). All biopsies were scored, blinded to the patient's identity and clinical condition, for individual histological features and for NASH stage and grade. Initial biopsies demonstrated NASH in 23 patients and steatosis in 12 patients. Repeat biopsies were taken at 25.6 ± 10 months (range, 9–51 months) after surgery.* ***Results:*** *Mean weight loss was 34.0±17 kg, and percentage of excess weight loss was 52±17%. There were major improvements in lobular steatosis, necroinflammatory changes, and fibrosis at the second biopsy (P<.001 for all). Portal abnormalities remained unchanged. Only four of the repeat biopsies fulfilled the criteria for NASH. There were 18 patients with an initial fibrosis score of 2 or more compared with 3 patients at follow-up (P < .001). Those with the metabolic syndrome (n = 23) had more extensive changes before surgery and greater improvement with weight loss.* ***Conclusion:*** *Bariatric surgery improves steatosis, necroinflammatory activity and hepatic fibrosis in patients with morbid obesity and NASH. It is followed by a dramatic improvement or normalization of liver histological abnormalities in the great majority of the patients.*

Keywords: *Morbid obesity, gastric bypass, sleeve gastrectomy, liver histology, non-alcoholic fatty liver disease, hepatic steatosis.*

INTRODUCTION

Obesity is a significant health problem and is on the rise in today's society. As obesity rises, so do associated co-morbidities, which include nonalcoholic fatty liver disease (NAFLD). As the body mass index (BMI) increases, so does the prevalence of NAFLD [1].

In obese individuals undergoing bariatric surgery, NAFLD is seen in 75% to 100% of cases. NAFLD includes a spectrum of liver abnormalities, which ranges from benign simple steatosis to nonalcoholic steatohepatitis (NASH), which in some cases progresses to hepatic cirrhosis [2].

The more progressive forms of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH) and associated hepatic fibrosis, are strongly associated with obesity and metabolic syndrome. As a result of the rising prevalence of obesity, liver disease may become the most common liver disorder in developed countries. On the basis that obesity is a principal factor in the pathogenesis of NAFLD, it would be expected that weight loss should be therapeutic.[3]

Current management of NAFLD includes weight loss through lifestyle modifications, as well as pharmacologic treatment that targets NAFLD pathogenesis. Nonetheless, in those who are obese, weight loss through lifestyle modification may be ineffective, and thus other weight loss strategies may be considered.[4]

Bariatric surgery is the most effective surgical procedure to achieve major and permanent loss of weight in these patients. As a consequence, the histological abnormalities of the liver could regress to a normal or close to normal condition after bariatric surgery.[5]

Current research suggests that bariatric surgery is effective at improving obesity-related co-morbidities as well as sustained long-term weight loss. However, the effect on liver

histology, specifically NASH and fibrosis, has shown conflicting results. Also, for those with persistent NAFLD or NASH post surgery, it is unclear what factors are associated with persistent histologic abnormalities. [6,7]

In 2005, Kleiner et al.[8]. described the nonalcoholic steatohepatitis (NASH) activity score (NAS), a tool originally intended to quantify changes in NAFLD in patients undergoing therapeutic trials. Strictly speaking, the diagnosis of NASH is made histologically, in patients with no history of significant alcohol use, by a characteristic pattern of liver steatosis, inflammation, and hepatocellular ballooning.

The scoring system comprised 14 histological features, 4 of which were evaluated semi-quantitatively: steatosis (0-3), lobular inflammation (0-2), hepatocellular ballooning (0-2), and fibrosis (0-4). Another nine features were recorded as present or absent. An anonymized study set of 50 cases (32 from adult hepatology services, 18 from pediatric hepatology services) was assembled, coded, and circulated.[9]

The purpose of the present prospective study was to determine the potential of histologic Improvement of NAFLD in patients with obesity after bariatric surgery based on standardized NAS (NAFLD Activity Score).

PATIENTS AND METHODS

Patients with a body mass index of more than 35 kg/m^2 who had significant medical, physical, or psychosocial disabilities are considered for entry

into the program. All patients undergo extensive preoperative assessment that includes a careful assessment of alcohol consumption, anthropometric measurements, and laboratory tests. Laboratory tests include liver function

tests, fasting lipid profile, fasting plasma glucose, fasting insulin, C-peptide, glycosylated hemoglobin A1c (HbA1c) and hepatitis B and C serological analysis. Investigations were performed to exclude hemochromatosis, 1-antitrypsin deficiency, Wilson disease, or autoimmune liver disease if indicated on the liver biopsy.

Patients were excluded from the NAFLD study if they had a history of alcoholism, consumed more than 200 g of alcohol per week, had evidence of hepatitis B or C, were taking known hepatotoxic medications, or had a history of or finding consistent with another specific liver disease.

At the time of the second biopsy, the clinical assessment and anthropometric and biochemical measures were repeated.

All index liver biopsies were taken at the time of laparoscopic sleeve gastrectomy (14 patients) and Laparoscopic OAGB (22 patients), during the period from 1/9/2013 until 1/9/2017, and a total of 197 unselected biopsies were obtained.

Follow-up biopsies were obtained either at the second laparoscopic procedure or as a percutaneous biopsy. There were 19 patients (9.6%) who had a second laparoscopic procedure and consented to a liver biopsy at that time thirteen of these had laparoscopic cholecysectomy. six were obtained at the time of laparoscopic revisional surgery ,two of them for gastric twist and the four for conversion of sleeve gastrectomy to OAGB for intolerable reflux symptoms.

All eligible patients having a laparoscopic procedure agreed to the follow-up biopsy. The remaining 17 patients agreed to have percutaneous liver biopsies because of concern regarding their index biopsy that showed NASH and centrilobular fibrosis of stage 2 or more. These 17 patients were from a group

of 23 (11.7%) selected for rebiopsy on clinical grounds, because the effect of weight loss on the more advanced forms of NAFLD, especially fibrosis, is unclear.

Five declined the opportunity of biopsy, and one patient had emigrated and could not be contacted. All index liver biopsies and intraoperative follow-up biopsies were performed percutaneously under laparoscopic view as a routine part of the operative procedure as previously described.

Nonoperative specimens were obtained percutaneously with the assistance of ultrasound guidance. Biopsy samples were obtained using a 14-gauge 200-mm Temno Biopsy needle. Adequacy of the biopsy was assessed macroscopically, and an additional core was taken if a specimen of less than 8 mm in length was obtained. All biopsies contained at least eight portal tracts.

Informed written consent was obtained from all patients at the time of the index biopsy. Informed written consent also was obtained from

all subjects before the second biopsy, and the study was conducted conforming to the ethical guidelines.

Preoperative excess weight was calculated as baseline weight (kg) and percentage of excess weight loss was calculated by dividing the weight change between paired biopsies by the excess weight before surgery, multiplied by 100.

Histological Assessment:

All liver biopsy specimens were stained with hematoxylin and eosin, silver reticulin, Masson trichrome, and Sirius red for collagen and Perls stain and ubiquitin, an immunostain demonstrating Mallory bodies.[10]

All sections were number coded such that the pathologist and observer performing the histological scoring were blinded to the patient identity, clinical condition, biochemical data and whether it was a biopsy from before weight loss or after weight loss. The 72 sets of biopsies slides were examined in a random order.

Histological Scoring:

A20 x 25 mm wedge of the liver was excised and immediately fixed in 10% formalin. The specimens were embedded in paraffin and block sections were cut at intervals of 5 mm. All sections were stained with hematoxylin and eosin, Van Gieson staining and Peris staining. All liver samples were examined by a pathologist specialized in liver disease blindly, i.e. without knowing to which patient the sample belonged. The parameters analyzed included the presence, severity, type and localization of fat, and the presence or absence of fibrosis and cirrhosis.

Finally, all were graded and staged for NASH according to the system proposed at the American Association for the Study of Liver Diseases single topic conference in September 2002.[11] (Table 2).

The pathologists first diagnosed NASH, then determined NAS and graded the severity of necroinflammation activity using the Brunt score.6 The Brunt score

is defined on a 3-step scale: mild (grade 1), moderate (grade 2), and severe (grade 3). The NAS, defined as the unweighted sum of scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2), ranging from 0 to 8, was also evaluated for the histologic follow-up of NASH after bariatric surgery.[12]

The following definitions were employed, according to the histological criteria published by Brunt et al.[9]

- Mild steatosis = <33% of hepatocytes with fat vacuoles.
- Moderate steatosis = 33-66% of hepatocytes with fat vacuoles.
- Severe steatosis = >66% of hepatocytes with fat vacuoles.
- Steatohepatitis = morphological liver damage which can be seen in alcoholic or non-alcoholic liver disease (obesity, drugs, diabetes, etc.). It consists of the presence of steatosis plus hepatocellular, portal or lobar inflammation and eventual fibrosis.
- Cirrhosis = regeneration nodules surrounded by fibrous tissue.

Table 1. Criteria Used for Histological Scoring [12]

Steatosis	
0	<5% of parenchyma involved
1	5% to 25% of lobular parenchyma involved
2	25% to 50% of lobular parenchyma involved
3	50% to 75% of lobular parenchyma involved
4	>75% of lobular parenchyma involved
Cellular injury	
Mallory bodies	
0	No Mallory bodies
1	Fewer than two in 10 to 20 X fields
2	More than two in 10 to 20 X fields
Ballooning degeneration	
0	Nil
1	Limited to zone 3 and affecting <50% of lobules
2	More extensive changes
Lobular inflammation	
0	No inflammation
1	Sparse zone 3 inflammation (less than one focus per lobule)
2	Mild focal zone 3 inflammation (1 to 2 foci per lobule)
3	Notable zone 3 inflammation (3 to 4 foci per lobule)
4	Severe zone 3 inflammation (>4 foci per lobule)
Portal inflammation extent	
0	No portal inflammation
1	Portal inflammation of less than 25% of portal tracts
2	Portal inflammation between 25% and 50% of tracts
3	Portal inflammation between 50% and 75% of tracts
4	Portal inflammation of greater than 75% tracts
Portal inflammation intensity	
0	Normal connective tissue
1	Perivenular and pericellular fibrosis limited to zone
2	Perivenular and pericellular fibrosis confined to zone 2 and 3
3	Bridging or extensive fibrosis with architectural distortion; no obvious cirrhosis
4	Cirrhosis
Portal fibrosis	
0	No portal inflammation
1	Portal fibrosis of less than 25% of portal tracts
2	Portal fibrosis of between 25% and 50% of tracts
3	Portal fibrosis of between 50% and 75% of tracts
4	Portal fibrosis of greater than 75% tracts

Table 2. Summary of Grading and Staging for NASH as Proposed by the American Association for the Study of Liver Diseases Single Topic Conference[13]

Grade	
Grade 1, mild	Steatosis in 33% to 66% of lobules, occasional ballooning degeneration in zone 3, mild lobular inflammation with or without mild portal inflammation
Grade 2, moderate	Steatosis, ballooning present in zone 3, lobular inflammation with polymorphs in association with ballooned hepatocytes, pericelluar fibrosis, or both, with or without mild chronic inflammation; none, mild, to moderate portal inflammation
Grade 3, sever	Steatosis: usually > 66%, marked ballooning especially zone 3, scattered lobular acute and chronic inflammation, plus mild to moderate portal inflammation
Stage	
1	Perivenular and pericellular fibrosis limited to zone 3
2	Stage 1 plus focal or extensive portal fibrosis
3	Bridging fibrosis, focal or extensive
4	Cirrhosis with or without residual perisinusoidal fibrosis

Operative Technique

Laparoscopic Sleeve Gastrectomy: LSG is a vertically oriented gastrectomy that removes approximately 70 to 80 percent of the greater curvature of the stomach, resulting in the creation of a narrow gastric tube with a volume of approximately 150 to 200 mL based on the less distensible lesser curvature (figure 1) [(14)]. The remnant stomach after LSG is referred to as a sleeved stomach or simply "sleeve."

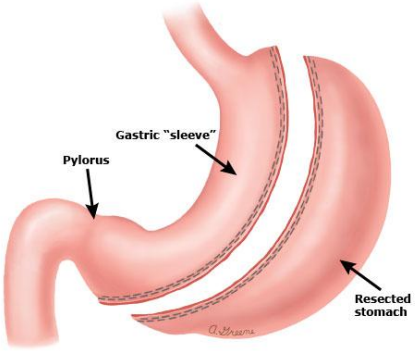

Fig. (1): In a sleeve gastrectomy, the majority of the greater curvature of the stomach is removed and a tubular stomach is created.

Laparoscopic OAGB: [(15)] Under general anesthesia, the patient is placed in supine french position with the legs spread apart. The operating surgeon is positioned between the patient's legs, the assisting surgeon at the left, and the camera assistance to the right side of the patient. After placement of supra- umbilical skin incision,just to the left side of the midline, insertion of visi-port with the camera inside till access the peritoneal cavity. Pneumoperitoneum is attained with CO2 under pressure of 12–15 mmHg. Two 12-mm trocars are inserted for the surgeon and two 5-mm trocars are inserted one for the assistant and one for self-retaining laparoscopic liver retractor. Initially, a long vertical gastric pouch is formed was formed using endo-staplers (EchelonFlex Endoscopic Articulating Linear Cutter, Ethicon Endo-Surgery Inc.The pouch is calibrated with a 40F bougie,and fashioned to be flobby in patient with BMI<32kg/m2,starting by one horizontal stapler at the level of the crow's foot (60mm loaded with green cartridges) and then 4-5 vertical staplers upward to the angle of His (60mm loaded with one green then blue cartridges), excluding the gastric fundus. Haemostatic clips were used to control intraoperative staple line bleeding of the gastric tube. After formation of the gastric pouch, the small intestine is counted up distal from the ligament of Treitz down to the caecum, the roux limb is fashioned to be 25% of the total bowel length with a minimum of 250 cm common channel then an anti-reflux continuous anchoring sutures between gastric pouch and the ante-mesenteric border of the small bowel is applied,. Then gastric and jejunal-hole is obtained for introducing the endo-stapler to establish a side-to-side, ante-colic, isoperistaltic anastomosis between gastric pouch and efferent limb. The stoma diameter is fashioned to be 3.5-4.5 cm,using 60mm cartridge endo-staplers (Echelon Flex),nasogastric tube is inserted passing the site of anastomosis to the efferent limb, then the stoma is closed using Vicryl© 0/2 endostitch sutures in 2 layers. Intraoperative methylene blue test for leak is performed then intraperitoneal nilton abdominal tube drain 20F is inserted.

Statistical Analysis:

Continuous demographic and anthropometric variables were expressed as mean ± SD change with between biopsies assessed using the paired Student t test. Histologic scoring and features were treated as ordinal categorical variables. Any change in scoring between index and second biopsies was assessed using the nonparametric Wilcoxon signed ranks test. All laboratory measures were expressed as median ± interquartile range, and changes were assessed using the Wilcoxon

signed ranks test. Correlation between ordinal or continuous variables was performed using Spearman-rho coefficients. The chi-square method (Fisher exact test) was used to test the significance of differences between proportions and categorical variables. Multivariate analysis was tested using binary logistic regression (forward and backward), and some β-coefficients have been shown.

SPSS statistical software (SPSS Inc., Chicago, IL) was used for statistical analysis. A P value of less than 0.05 was considered statistically significant.

RESULTS

There were 36 patients with paired biopsies. This represents 18.3% of the 197 unselected patients from whom liver biopsy samples were obtained during the defined period.

Patient characteristics are shown in Table 3. Paired biopsies were assessed in 36 (11 male and 25 female) patients.

The second biopsy was obtained 25.6 ± 11 months (range, 9–51 months) after surgery. The mean weight loss at this time was 34.0 ± 17.0 kg (range, 8–68.5 kg).

Other clinical, demographic, and weight loss data, including the percentage of excess weight lost, are shown in Table 3.

Index biopsies had a mean of 13.8 ± 4.8 portal tracts (range, 8–30 portal tracts), and second biopsies had a mean of 15.5 ± 5.1 portal tracts (range, 8–28 portal tracts).

Weight loss was accompanied by significant favorable changes in anthropometric measures, including waist, hip, and neck circumferences and waist to- hip ratio (Table 3).

Scores for steatosis, lobular inflammation, centrilobular fibrosis, Mallory bodies, and ballooning degeneration all improved significantly with weight loss. There were no significant changes in any of the scores for portal fibrosis

or inflammation (Table 4). There were no histological features that changed unfavorably with weight loss. (Figure 2).

Table (3): Changes in anthropometric measurements between the patients first and second liver biopsy (n = 36)

	Pre weight loss (mean, median, %)	**With weight loss (mean, median, %)**
BMI (kg/m^2)	47 ± 10.6	34.0 ± 5.5
Weight (kg)	134.8 ± 26	99.8 ± 17.2
Percentage of excess weight lost		51.6 ± 17.3
Waist (cm)	132.1 ± 17.4	108.3 ± 15.4
W:H ratio	0.93 ± 0.10	0.87 ± 0.97

Table (4): Histologic Scores for the 36-Paired Biopsies Reported Blinded to the Patient's Identity, Clinical Features and Timing

Feature	**Scores**					**P value**
	0	**1**	**2**	**3**	**4**	
Steatosis						
A	1	3	6	12	14	< 0.001
B	21	9	2	3	1	
Lobular inflammation						
A	12	5	8	8	3	<0.001
B	25	8	3	0	0	
Fibrosis						
A	13	5	7	10	1	<0.001
B	29	4	1	1	1	
Mallory bodies						
A	15	9	12			<0.001
B	34	1	1			
Ballooning degeneration						
A	10	12	14			<0.001
B	27	9	0			
Portal inflammation						
A	1	18	4	5	8	0.9
B	2	13	8	10	3	
Portal fibrosis						
A	13	12	4	4	3	0.34
B	11	10	5	5	5	

NASH Grade and Stage:

All specimens were scored for NASH grade and stage using the American Association for the Study of Liver Diseases proposed method (Table 5).[11]

Table (5): American Association for the Study of Liver Diseases Proposed Scoring for the Grade and Stage of NASH

	Scores					P value*
	0	**1**	**2**	**3**	**4**	
Grade						
A†	12	5	6	13		< 0.001
B†	30	4	2			
Stage						
A†	13	3	9	10	1	< 0.001
B‡	29	2	2	2	1	

*Calculated using the Wilcoxon signed rank test.
†Before weight loss or index biopsy.
‡Follow-up biopsy.

Table (6): Correlation Between the Metabolic Syndrome Ordinal Score Before Weight Loss and Features in Index Biopsy and the Change in Histological Scores Between Biopsies

	Metabolic syndrome 1,2 or 3	
	Correlation index biopsy score	**Correlation with change in score between biopsies**
Steatosis	0.56†	- 0.17
Lobular inflammation	0.56†	- 0.52†
Fibrosis	0.38*	-0.40*
Mallory bodies	0.41*	-0.52†
Ballooning degeneration	0.48†	-0.33*
Portal inflammation	0.18	-0.11
Portal fibrosis	0.30	-0.16
NASH grade	52†	-0.53†
NASH stage	0.37*	-0.38*

*Spearman correlation was significant at the 0.05 level (two-tailed).
†Spearman correlation was significant at the 0.01 level (two-tailed).

There were 24 patients with a score of at least 1 for grade or stage before surgery, compared with 9 such patients at follow-up ($P < 0.001$).

We classified subjects as having NASH if their biopsy scored at least 1 for both grade and stage. There were 23 subjects with NASH in their index biopsy, 20 (87%) of whom had metabolic syndrome.

By contrast, only four of the follow-up biopsies demonstrated NASH ($P < 0.001$); in two, the second biopsy had an improved combined grade and stage score, and in two, there was no change.

Thus, in this series, 82% of subjects had resolution or remission of NASH with weight loss, 9% demonstrated improvement, and 9% were unchanged. The median changes in NASH grade and NASH stage between paired biopsies fell by a score of 1.0.

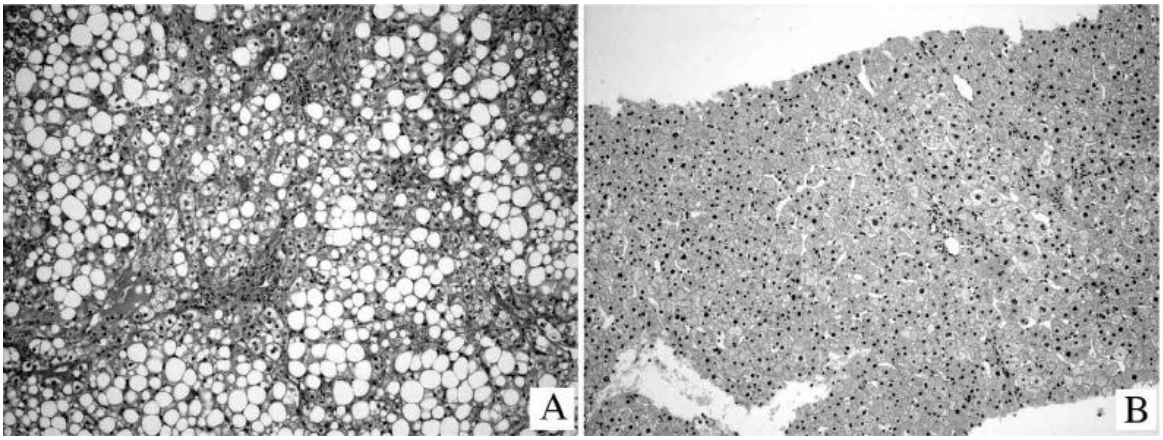

Fig. (2): Photomicrograph of the liver biopsies from the same patient. A) first biopsy: note the intense steatosis and steatohepatitis. B) second biopsy: note the absence of steatosis and steatohepatitis. HE, 100X.

DISCUSSION

In this study, we demonstrated that the key features of NAFLD and NASH improve or resolve dramatically with weight loss. These key features include zone 3 features of steatosis, necroinflammatory change, and fibrosis. Greater improvement is seen in those selected subjects who had been diagnosed with metabolic syndrome before surgery. In addition, individual histological abnormalities that correlated with metabolic syndrome improved significantly more with weight loss in those with metabolic syndrome.

The histological features of NASH resolved or remitted in 82% of patients. These findings support the hypothesis that, in these selected obese subjects, obesity and metabolic syndrome are causally associated with the liver condition observed [17].

Our findings also assist in validation of which specific histological features are associated with obesity- and metabolic syndrome-associated NASH. Our results demonstrate major improvement in necroinflammatory activity and fibrosis with weight loss, findings that have not always been reported consistently.

Our study confirmed that NASH is strongly related to obesity. Nonetheless, across the range of NAS scores, there was a significant overall decrease, giving reason to believe that even the more severe entity, NASH, is likely to improve after bariatric surgery.

The histological abnormalities of the liver among patients with morbid obesity at bariatric surgery are well known and described. The number of patients evaluated during bariatric surgery, by taking liver samples, have varied from study to another.[18,19]

The method chosen to achieve weight loss may be important. Studies involving diet, lifestyle, and exercise interventions often are shorter-term studies and usually do not achieve such substantial sustained weight loss.[120,21]

Weight loss programs involving low- or very low-calorie diets typically are followed by some weight gain, and biopsies taken during such a phase may not truly represent the effects of weight loss. At a mean duration of 25 months after surgery, most of our patients not only have lost substantial weight but also are relatively weight stable.[22]

In different studies, the incidence of histologic liver damage in the morbidly obese patients is very high. However, no reliable biochemical data can identify patients with severe liver damage, to obviate the need for liver biopsy for diagnosis and staging of the disease. It has been shown that routine liver biopsy documented significant liver abnormalities compared to selective liver biopsies. [23]

Therefore, evaluation of liver histology late after sleeve gastrectomy and gastric bypass or any other bariatric procedures, is important, in order to determine whether significant loss of weight is associated with significant improvement in the pathologic appearance of the liver.

Assessment of the biopsy specimens also may hold some clues. Few studies have reported a wide range of features, and rarely are individual features scored independently. Steatosis may be such an overwhelming feature in some of the specimens obtained before weight loss that a careful assessment of necroinflammatory and portal tract changes may be overlooked. A dramatic reduction in steatosis may enhance or unmask the view of inflammatory cells or portal changes.

Neuschwander-Tetri [11] carefully explored the histologic changes induced by the use of the intracellular insulin-sensitizing medication, Rosiglitazone, on patients with NASH. They describe significant improvements in zone 3 histologic features, including necroinflammatory changes and fibrosis. These reported changes are entirely consistent with our findings, and the persistence of mild portal inflammation is a common feature. This suggests that these portal changes may not be associated directly with metabolic syndrome or insulin resistance. It is interesting that weight loss and improved insulin sensitivity without weight loss have similar effects on liver histological features, suggesting a common mechanism.

In a previous study, the results indicated that after a rapid and considerable loss of weight as a consequence of gastric bypass, liver histological abnormalities which were present in 94% of the patients before surgery, improved significantly in 87% of the patients, reaching normal liver histology in 67% of them. [24]

LSG surgery has several features that allow us to look relatively cleanly at the effect of significant weight loss on NASH. Diversionary surgical weight procedures with significant malabsorption may lead to nutritional deficiencies and alterations of intestinal flora, potentially confounding this effect.[25]

Bariatric surgery represents an important treatment option for patients with NASH and obesity. For these patients, weight loss may be necessary but inadequate to reverse the histologic changes associated with this disease. For the majority of patients who have obesity and metabolic syndrome, bariatric surgery has been demonstrated to have a clear benefit in reducing all of the components of NASH, including steatosis, steatohepatitis, and fibrosis[27].

A recent report follows up patients after biliopancreatic diversion and describes a generally positive benefit with weight loss, but some subjects had increased fibrosis that was related to lower albumin levels and uncontrolled diarrhea.[27]

CONCLUSION

In conclusion, we have demonstrated major improvement in the histological features of liver disease associated with obesity and metabolic syndrome with weight loss after bariatric surgery based on standardized NAS (NAFLD Activity Score). Further studies to define the appropriate window for safe and effective bariatric surgery in patients with NASH are needed.

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