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BRIEF ARTICLE

Surgically induced weight loss by gastric bypass improves non alcoholic fatty liver disease in morbid obese patients

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Abstract

AIM: To evaluate the effects of surgical weight loss (Roux-en-Y gastric bypass with a modified Fobi-Capella technique) on non alcoholic fatty liver disease in obese patients.

METHODS: A group of 26 morbidly obese patients aged 45 ± 2 years and with a body mass index > 40 kg/m^2 who underwent open surgical weight loss operations had paired liver biopsies, the first at surgery and the second after 16 ± 3 mo of weight loss. Biopsies were evaluated and compared in a blinded fashion. The presence of metabolic syndrome, anthropometric and biochemical variables were also assessed at baseline and at the time of the second biopsy.

RESULTS: Percentage of excess weight loss was 72.1% ± 6.6%. There was a reduction in prevalence of metabolic syndrome from 57.7% (15 patients) to 7.7% (2 patients) ($P < 0.001$). Any significance difference was observed in aspartate aminotransferase or alanine aminotransferase between pre and postsurgery. There were improvements in steatosis ($P < 0.001$), lobular ($P < 0.001$) and portal ($P < 0.05$) inflammation and fibrosis ($P < 0.001$) at the second biopsy. There were 25 (96.1%) patients with non alcoholic steatohepatitis (NASH) in their index biopsy and only four (15.3%) of the repeat biopsies fulfilled the criteria for NASH. The persistence of fibrosis (F > 1) was present in five patients at second biopsy. Steatosis and fibrosis at surgery were predictors of significant fibrosis postsurgery.

CONCLUSION: Restrictive mildly malabsorptive surgery provides significant weight loss, resolution of metabolic syndrome and associated abnormal liver histological features in most obese patients.

Key words: Non alcoholic fatty liver disease; Bariatric surgery; Obesity; Non alcoholic steatohepatitis

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INTRODUCTION

The term non alcoholic fatty liver disease (NAFLD) includes a spectrum of fatty liver diseases ranging from simple steatosis to steatohepatitis [non alcoholic steatohepatitis (NASH)] and cirrhosis[1]. The more progressive forms of NAFLD have been related to metabolic syndrome and obesity[2]. The epidemic of obesity has increased the prevalence of NAFLD and it is already the most common liver disorder in developed countries. Morbid obese patients have a high proportion of NAFLD. Most patients undergoing bariatric surgery have varying degrees of steatosis: as many as 36% have NASH and up to 4% have unsuspected cirrhosis. Only a small percentage of patients undergoing bariatric surgery have normal hepatic histology[3].

The optimal treatment of NASH has yet to be elucidated. In general, efforts have been developed to correct or improve insulin resistance and, in obese patients, weight loss has been prescribed. The effects of weight loss on NAFLD lesions have been studied and the reported effects of this therapy have been variable. Diet induced weight loss improved steatosis but did not always demonstrate an effect on histological parameters since in most studies repeated liver biopsy was not performed[3-8].

Also the effect of bariatric surgery could be confounding. Initially, it was described that rapid weight loss can exacerbate steatohepatitis in morbidly obese patients, especially after bariatric surgery[9]. This effect was more marked when malabsorptive procedures, like jejunoileal bypass or biliopancreatic diversion, were used. More recently, restrictive procedures, such as laparoscopic adjustable gastric banding, have demonstrated significant improvement in histopathological scoring[10-12], but in some studies the improvement in steatosis was accompanied by a progression of lobular inflammation[13].

We have less information about the effects on patients when mixed procedures were used[14]. The most frequently performed is Roux-en-Y gastric bypass, largely restrictive and mildly malabsorptive. In this procedure, the restriction is induced by a small neogastric pouch and a tight stoma and malabsorption by Roux-en-Y configuration of the small intestine[15]. The purpose of this study was to determine whether significant weight loss achieved through a standard mixed procedure - Roux-en-Y gastric bypass[16,17] - of bariatric surgery resulted in improvements in liver histopathology.

MATERIALS AND METHODS

Since May 2004, a prospective protocol has been followed for patients with morbid obesity that had a Roux-en-Y gastric bypass. Up to September 2005, twenty-six obese patients with a body mass index of more than 40 kg/m^2 who had significant medical, physical or psychosocial disabilities were considered for entry into the study. All patients underwent extensive preoperative assessment that included alcohol consumption, anthropometric measurements and laboratory tests. Laboratory tests included liver function tests, lipid profile, fasting plasma glucose, fasting insulin and hepatitis B and C serological analysis. Diagnosis of type 2 diabetes was based on the American Diabetes Association criteria[18]. Insulin sensitivity was estimated using the homeostatic model assessment method (HOMA)[19]. A diagnosis of metabolic syndrome was based on Adult Treatment Panel Ⅲ criteria[20]. At the time of the second biopsy, the clinical assessment and anthropometric and biochemical measures were repeated. Percentage of excess weight loss was calculated by dividing the weight change between paired biopsies by the excess weight before surgery, multiplied by 100.

Any patient with a history of alcoholism, consuming more than 200 g of alcohol per week, with evidence of hepatitis B or C or with a history of another specific liver disease, was included in the study.

An open Roux-en-Y gastric bypass with a modified Fobi-Capella technique (ring 7 cm; alimentary limb 225 cm; biliopancreatic limb 60 cm) was performed in all patients.

An index biopsy was taken at the time of surgery with a Hepafix needle. In all patients, a follow up biopsy was obtained as a percutaneous biopsy using a Hepafix needle. All biopsies were at least 2 cm in length and contained at least eight portal tracts. Informed written consent was also obtained from all patients at the time of the index biopsy as part of an approved prospective study of bariatric surgery. Informed written consent also was obtained from all subjects before the second biopsy and the study was conducted according to the ethical guidelines of the Helsinki Declaration.

All liver biopsy specimens were stained with hematoxylin eosin, picrosiriums for fibrosis and periodic acid Schiff (PAS) with diastase to help clarify the degree of inflammation.

Table 1 Criteria used for histological scoring[21]

Steatosis:
0 : None
1: up to 33%
2: 33%-66%
3: > 66%
Hepatocyte ballooning
0: None
1: Occasional, Zone 3
2: "Obvious" Zone 3
3: Marked, predominantly Zone 3
Mallory bodies
0: No Mallory bodies
1: Fewer than two in 10 to 20 × fields
2: More than two in 10 to 20 × fields
Glycogenated nuclei
0: Absent
1: Occasional
2: Several
Lobular inflammation (inflammatory foci per 20 × with a 20 × ocular)
0: None
1: 1 to 2/20
2: Up to 4/20
3: More than 4/20
Portal inflammation
0: None
1: Mild
2: Moderate
3: Severe
Fibrosis score:
Stage 0: No fibrosis
Stage 1: Zone 3 perisinusoidal/pericellular fibrosis; focally or extensively present
Stage 2: Zone 3 perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis
Stage 3: Zone 3 perisinusoidal/pericellular fibrosis and portal fibrosis with a focal or extensive bridging fibrosis
Stage 4: Cirrhosis

A single hepatopathologist (HA), blinded to the patient, clinical and laboratory data and to whether the biopsy was the pre or post operative biopsy, examined all tissue sections at the same time and assessed liver histology using a systemic approach of necroinflammatory grading and fibrosis staging as described by Brunt *et al*[21] and modified by Kleine *et al*[22]. Individual histological features were observed and scored separately (Table 1): Steatosis: 0: None; 1: Up to 33%; 2: 33%-66%; 3: > 66%. Hepatocyte ballooning: 0: None; 1: Occasional, Zone 3; 2: "Obvious" Zone 3; 3: Marked, predominantly Zone 3. Mallory bodies: 0: No Mallory bodies; 1: Fewer than two in 10 to 20 × fields; 2: More than two in 10 to 20 × fields. Glycogenated nuclei: 0: Absent; 1: Occasional; 2: Several. Lobular inflammation (inflammatory foci per 20 × with a 20 × ocular): 0: None; 1: 1 to 2/20; 2: Up to 4/20; 3: More than 4/20. Portal inflammation: 0: None; 1: Mild; 2: Moderate; 3: Severe. Fibrosis score: Stage 0: No fibrosis; Stage 1: Zone 3 perisinusoidal/pericellular fibrosis; focally or extensively present; Stage 2: Zone 3 perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis; Stage 3: Zone 3 perisinusoidal/pericellular fibrosis and portal fibrosis with a focal or extensive bridging fibrosis; Stage 4: 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[23].

Also, for each patient, the following variables were assessed at baseline and at the moment of second liver biopsy: age, waist circumference, weight, percentage excess weight loss, body mass index (BMI), alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, gamma-glutamyl transferase level, bilirubin level, serum triglyceride level, cholesterolemia, serum high density lipoprotein cholesterol, serum low density lipoprotein cholesterol, blood glucose level, fasting insulin level, HOMA, steatosis amount, portal and lobular inflammation, fibrosis score and grade of NASH. The relationship between persistence of liver fibrosis after surgery (F > 1) and various risk factors was studied using a univariate analysis. In the univariate analysis, 2 groups were compared according to the presence or absence of significant fibrosis (F > 1) in the liver biopsy.

Statistical analysis of clinical and laboratory data was assessed using a paired samples *t* test. For histological comparisons pre-surgery and post-surgery, paired *t* tests were confirmed with Wilcoxon signed rank tests.

RESULTS

There were 26 patients (7 male and 19 female) with paired biopsies. Patient characteristics are shown in Table 2. There were no patients with cirrhosis and no complications from the gastric bypass or deaths during this study. The second biopsy was obtained 16.3 ± 3 mo (range: 12-22 mo) after bariatric surgery and no complications (bleeding, biloma, *etc*.) were observed during this postoperative percutaneous liver biopsy.

The percentage of excess weight loss was 72.1% ± 6.6% and the average rate of weight loss was 0.69 ± 0.22 kg/wk. Other clinical demographic and weight loss data are shown in Table 1. Weight loss was accompanied by significant favorable changes in anthropometric measures, significant decreases in blood pressure and major improvements in biochemical markers of metabolic syndrome, plasma glucose, insulin levels, insulin sensitivity and cholesterol levels (Table 1). Fifteen of the 26 patients (57.7%) fulfilled criteria for metabolic syndrome and only 2 (7.7%) fulfilled these criteria at the follow-up. Preoperatively, 7 (27%) patients had abnormal alanine aminotransferase or aspartate aminotransferase (> 0.58 μkat/L); postoperatively only 3 had abnormal alanine aminotransferase or an aspartate aminotransferse levels (> 0.58 μkat/L). There were no significant differences in aminotransferase levels with weight loss.

Histopathological results

Significant histopathological improvement was seen in steatosis ($P < 0.001$), ballooning degeneration ($P < 0.001$),

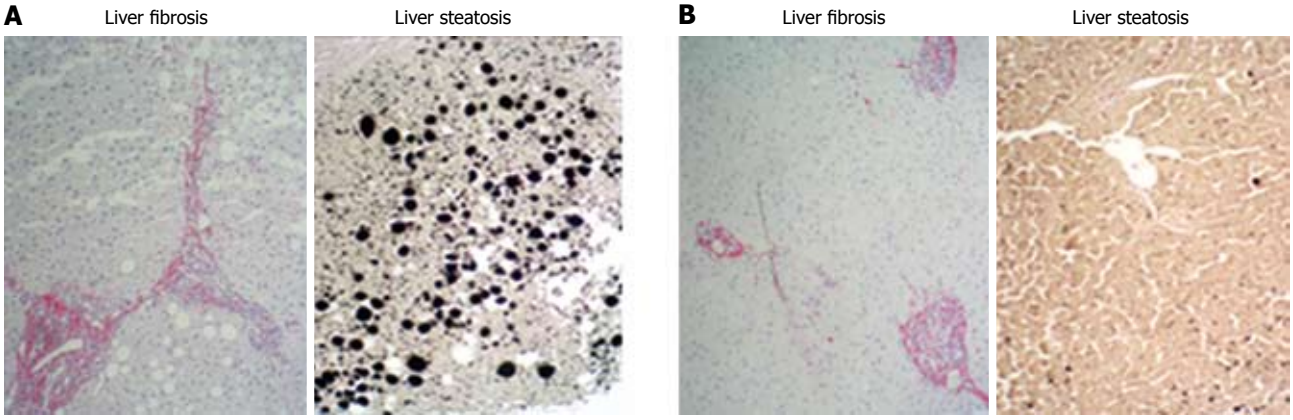

Figure 1 Marked improvement of liver fibrosis (left panel; picrosirius stain, ×10) and liver steatosis (right panel; osmium stain ×20) before (A) and after (B) bariatric surgery.

Table 2 Changes in anthropometric measurements and biochemistry between the patients' first and second liver biopsy

	Pre bariatric surgery	Post bariatric surgery	*P* value
Weight (kg)	130.8 ± 20.1	82.3 ± 13.7	< 0.001
BMI (kg/m^2)	49.3 ± 4.8	30.9 ± 4.3	< 0.001
% excess weight loss		72.1 ± 6.6	
Waist (cm)	137.1 ± 12.6	97.3 ± 11.0	< 0.001
Diabetic (%)	12 (46.1)	6 (23)	0.14
Hypertensive (%)	17 (65.4)	7 (26.9)	0.012
Metabolic syndrome	15 (57.7)	2 (7.7)	< 0.001
Cholesterol (mmol/L)	5.44 ± 1.00	4.29 ± 0.85	< 0.001
HDL-C (mmol/L)	1.24 ± 0.21	1.40 ± 0.19	0.005
LDL-C (mmol/L)	3.47 ± 0.76	2.46 ± 0.75	< 0.001
Triglycerides (mmol/L)	1.60 ± 0.63	0.93 ± 0.29	< 0.001
AST (μkat/L)	0.35 ± 0.09	0.36 ± 0.17	0.862
ALT (μkat/L)	0.49 ± 0.20	0.37 ± 0.31	0.143
GGT (U/L)	40.2 ± 17.4	19.2 ± 12.8	< 0.001
Fasting glucose (mmol/L)	6.46 ± 2.3	4.96 ± 0.55	0.001
Insulin (pmol/L)	235.2 ± 7.2	56.1 ± 7.2	0.006
Insulin resistance (HOMA)	9.99 ± 13.3	1.8 ± 1.4	0.006

BMI: Body mass index; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; HOMA: Homeostatic model assessment method.

Table 3 Histological scores for the 26-paired biopsies

	Scores					*P* value
Feature	0	1	2	3	4	
Steatosis						< 0.001
Pre	0	13	8	5	-	
Post	24	2	0	0	-	
Ballooning degeneration						< 0.001
Pre	10	8	7	1	-	
Post	25	1	0	0	-	
Mallory bodies						0.005
Pre	18	8	0			
Post	26	0	0			
Glycogen nuclei						0.001
Pre	8	7	11			
Post	13	8	5			
Lobular inflammation						< 0.001
Pre	1	23	2	0		
Post	15	11	0	0		
Portal inflammation						0.05
Pre	1	23	2	0		
Post	7	19	0	0		
Fibrosis						0.001
Pre	1	17	6	2	0	
Post	9	12	4	1	0	

Mallory bodies ($P = 0.005$), glycogen nuclei ($P = 0.001$), lobular inflammation ($P < 0.001$), portal inflammation ($P = 0.005$) and fibrosis ($P < 0.001$) (Figure 1 and Table 3).

We classified subjects as having NASH if their biopsy scored at least 1 for both grade and stage. There were 25 patients (96%) with NASH in their index biopsy. By contrast, only 4 (15.3%) of the follow up biopsies demonstrated NASH ($P < 0.001$). Table 4 shows scoring for the grade and stage of NASH in liver biopsies performed at surgery and during follow up. None of the second biopsies revealed progression of grade or stage of liver disease.

The changes in steatosis are perhaps one of the more significant features in this analysis. Steatosis score improved overall by two or more grades in 12 patients and by one grade in 14 patients. Although portal inflammation improved significantly, it disappeared in only seven patients; after surgery, some degree of portal inflammation persisted in 19 patients.

Although the change in fibrosis was significant, it was not constant. Fibrosis score improved overall by two stages in 1 patient and by one stage in 10 patients. In 15 patients, fibrosis remained stable and we did not observe any patient with worsening of liver fibrosis (Figure 2). Eight patients had significant fibrosis (F > 1) before surgery. At the second liver biopsy, five patients still had significant fibrosis (Figure 3). In univariate analysis, patients with significant liver fibrosis after surgery had a significantly higher steatosis score, higher fibrosis score and lower AST level at the time of surgery than patients without (Table 5). After bariatric surgery, one of two patients with metabolic syndrome and none of the 6 patients with diabetes had a fibrosis score greater than 1 in the liver biopsy. There was no difference in the interval between

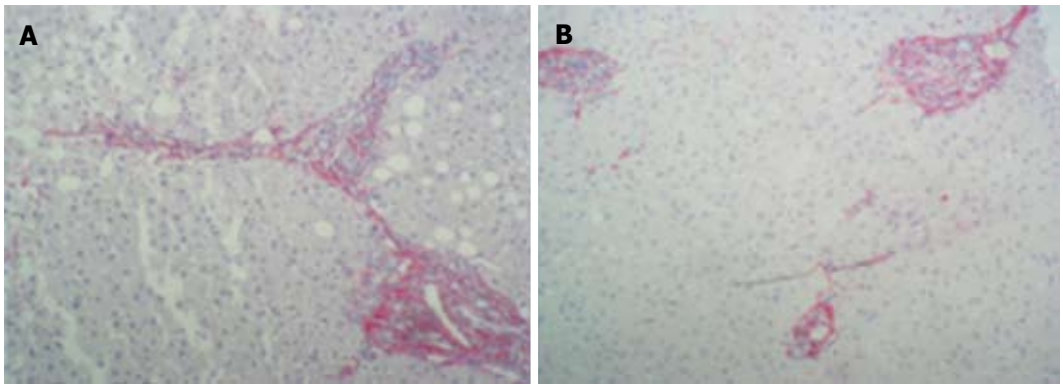

Figure 2 Persistence of liver fibrosis after bariatric surgery (picrosirius stain, ×10). A: At surgery; B: Post-surgery.

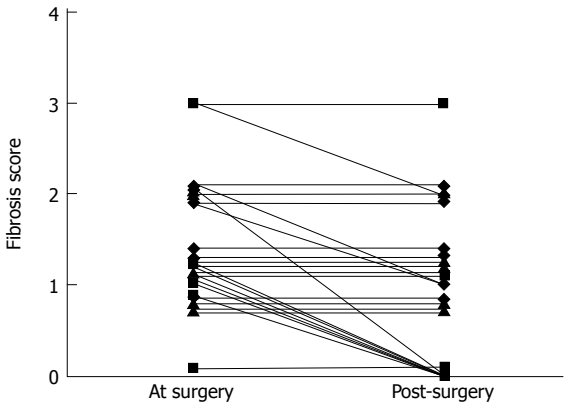

Figure 3 Evolution of fibrosis score in the liver biopsies of 26 patients with bariatric surgery.

surgery and biopsy in patients with or without significant fibrosis [432 ± 133 d *vs* 530 ± 122 d respectively, *P* = not significant (NS)]. Equally, there was no difference in the average rate of weight loss in patients with or without significant fibrosis (0.81 ± 0.26 kg/wk *vs* 0.66 ± 0.21 kg/wk respectively, *P* = NS).

DISCUSSION

In this study, we have demonstrated that, in patients with morbid obesity, weight loss induced by a mixed bariatric surgery (combination of malabsorptive and restrictive, Roux-en-Y gastric bypass with a modified Fobi-Capella technique) dramatically improved nonalcoholic fatty liver disease lesions observed in these patients.

There are various types of bariatric procedures. Initially, the most commonly used were primarily malabsorptive. Using these techniques, most of the obesity-related liver abnormalities did not improve, or even worsened. Jejunoileal bypass performed in the 1950-1970s was abandoned due to various complications, including significant hepatic lesions and even cirrhosis[24-26]. Numerous mechanisms, such as malabsorption of essential micronutrients, bacterial overgrowth and rapid weight loss with resulting massive influx of free fatty acids, have been implicated in the pathogenesis of NAFLD associated with jejunoileal bypass[27]. For example, Requarth *et al*[28] reported the long term morbidity after jejunoileal bypass in 453 patients and 24 of these developed acute liver failure (7%) and the 15 years probability of established cirrhosis was 8.1%.

More recently, restrictive or mixed techniques of bariatric surgery have been used. Lately, most of the published studies have focused on the effect of restrictive techniques on NAFLD. Thus, Dixon *et al*[10] used a laparoscopic adjustable banding technique that achieved a weight loss of around 50% and observed important improvements in steatosis, necroinflammatory changes and fibrosis.

The bariatric surgery technique used by us is mixed, restrictive and mildly malabsorptive. The techniques which, like ours, use a gastric bypass, produce a greater weight loss than gastric banding and also are longer lasting[29,30]. It would be interesting to know if these different types of surgical approaches are accompanied by similar effects on the treatment of liver lesions seen in obesity.

Using a bariatric surgery technique that combines restriction with mild malabsorption, we obtained a significant weight loss in patients. In addition, we have not only achieved a drastic remission of steatosis, but also improvements in lobular inflammatory activity and fibrosis. In our study, the percentage of excess weight loss (72%) was clearly superior to that observed in the Dixon study (52%), previously cited[10]. Although other studies have been done with techniques other than merely restrictive, good results have also been found in improvement of NAFLD[12,31].

It has been suggested that weight loss induced by malabsorptive procedures could disguise NASH improvements after bariatric surgery because, in some patients, impairment in liver fibrosis could be observed. This effect was observed in the study performed by Kral *et al*[32] that used biliopancreatic diversion. They found a constant improvement in metabolic syndrome but the effect on liver fibrosis varied. In their study, there was a frank improvement of fibrosis in patients with pre surgery advanced fibrosis (grades 1-2) and, in contrast, "*de novo*" fibrosis appeared in patients that did not have presurgery fibrosis. We have not observed this effect and the small number of samples in which we observed persistence of fibrosis was in those patients with a presurgery fibrosis greater than stage 1. The difference in the results can be

Table 4 Scoring for the grade and stage of non alcoholic steatohepatitis *n* (%)

	Scores				*P* value
	0	1	2	3	
Grade					
At surgery	1 (3.8)	12 (46.1)	11 (42.3)	2 (7.7)	0.001
Follow up biopsy	22 (84.6)	4 (15.4)	0 (0)	0 (0)	
Stage					
At surgery	1 (3.8)	17 (65.4)	6 (23.1)	2 (7.7)	0.001
Follow up biopsy	9 (34.6)	12 (46.1)	4 (15.4)	1 (3.8)	

Table 5 Factors associated with significant fibrosis (F > 1) after bariatric surgery

Variable	F 0-1 post surgery (*n* = 21)	F > 1 post surgery (*n* = 5)	*P* value
Mean steatosis score at surgery	1.5 ± 0.7	2.6 ± 0.5	0.002
Mean fibrosis score at surgery	1.1 ± 0.4	2.4 ± 0.5	< 0.001
Mean serum AST level at surgery (IU ± SD)	22.8 ± 11.6	11.6 ± 4.0	0.034

AST: Aspartate aminotransferase.

explained because Kral *et al*[32] found alcohol ingestion as a predictive factor of increasing fibrosis. Our series did not include alcoholic patients and this argues in favor of the fact that the increasing fibrosis seen in the Kral study was not related to the type of intervention, but to alcoholic ingestion post surgery.

In our study we saw a global improvement in portal fibrosis. Nevertheless, there were patients whose fibrosis did not improve; in 15 patients it remained stable. Barker *et al*[14] performed liver biopsy at surgery and postoperatively in 19 patients, mostly women without alcohol ingestion with a bariatric surgery technique similar to that used in our study, and found a frank improvement in fibrosis lesions, except in 4 patients whose lesions remained stable. Probably this slightly greater improvement in fibrosis can be explained by a longer interval between surgery and performance of the second biopsy. It was 21 mo in Barker's study and 16 mo in our work.

Similarly to Barker *et al*[14] and other studies about liver improvement of NASH with treatment[10,33], we also evidenced a persistence of portal inflammation. In most of our patients it was mild at surgery and significantly improved when it was analyzed globally; but in 19 patients some degree of portal inflammation persisted. This phenomenon is frequent and it has been suggested that these portal changes do not have a direct relationship with metabolic syndrome or insulin resistance[10,33].

When the factors that could predict persistence of significant liver fibrosis were analyzed, biochemical and clinical factors at the time of biopsies had low statistical power. The most important predictive factors were histological. Liver fibrosis and steatosis score at surgery were statistically associated with the persistence of significant fibrosis in liver biopsy post surgery. It has been demonstrated that steatosis at surgery and insulin resistance influence persistence of steatosis after bariatric surgery[34], but the influence of steatosis on the persistence of fibrosis has not been clearly demonstrated. In our work, we found that, not only liver fibrosis at surgery, but also steatosis score has an influence on the persistence of fibrosis. It is known that a fatty liver is more vulnerable to factors that lead to fibrosis[35] and in the presence of chronic liver diseases, steatosis may exacerbate liver injury[36]. The persistence of liver fibrosis in our patients mediated by various factors may be helped by the previous existence of a severe degree of steatosis.

Finally, patients with a persistence of significant fibrosis had a lower level of aminotransferases than those patients whose fibrosis was maintained or improved. This finding probably has low relevance, because in both groups aminotransferase levels were within normal range and it is also known that ALT values progressively decrease after BMI > 30 kg/m^2; therefore, it frequently happens that patients with morbid obesity have normal values of aminotransferase[27].

In conclusion, we have demonstrated that bariatric surgery, using a restrictive and mildly malabsorptive procedure, has a strong effect on improvement of liver abnormalities associated with non alcoholic fatty liver disease in the morbidly obese, although any significant changes were observed in aminotransferase enzymes.

COMMENTS

Background

Non alcoholic steatohepatitis (NASH) is one of the most common liver disease in patients with morbid obesity, and is associated with metabolic syndrome. The effects of the most current treatments for NASH (diet induced weight loss, bariatric surgery, *etc.*) are confounding. Therefore, it will be of interest to know the effects of Roux-en-Y gastric bypass on NASH.

Research frontiers

NASH is a very frequent disease affecting morbidly obese but it does not have an specific treatment to improve it, so the hotspot for NASH is to find a treatment for it.

Innovations and breakthroughs

The finding provides further evidence on the conclusions that Roux-en-Y gastric bypass associated weight loss enhances the resolution of metabolic syndrome and improves liver histological features in morbidly obese patients.

Applications

This paper, together with other related publications, can be collectively instructive to bariatric surgeons and nutritionists in their practice in treat morbidly obese patients.

Peer review

This paper shows interesting results even though the sample size is small. Perhaps the more interesting finding to highlight is the improvement in the fibrosis score after surgery. And it is a very interested study that discusses the benefits of surgically induced effects on obese patients with NAFLD.

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