OBES SURG (2012) 22:1044–1049
DOI 10.1007/s11695-011-0559-y

CLINICAL RESEARCH

Effect of Bariatric Surgery on Liver Fibrosis

Myriam Moretto · Carlos Kupski · Vinicius Duval da Silva · Alexandre V. Padoin · Cláudio C. Mottin

Published online: 23 November 2011

Abstract
Background Although bariatric surgery has been shown to improve hepatic steatosis in morbidly obese patients, the effect of weight loss on hepatic fibrosis has not been determined. Since the prognosis of patients with nonalcoholic fatty liver disease is closely related to the development of hepatic fibrosis, it is important to determine the hepatic histology of these patients after weight loss. We therefore evaluated the prevalence of hepatic fibrosis in morbidly obese patients undergoing bariatric surgery and assessed the correlation of histologic changes with weight loss.
Methods We retrospectively evaluated 78 morbidly obese patients who underwent gastric bypass. Liver biopsies were taken during surgery and after weight loss, and the correlations between histologic findings and hepatic fibrosis were determined.
Results Of the 78 patients, 35 (44.8%) had fibrosis at first biopsy, and 24 (30.8%) had hepatic fibrosis after weight loss, including 19 of the 35 patients (54.3%) with fibrosis at first biopsy and 5 of the 43 (11.6%) without hepatic fibrosis at first biopsy (P=0.027).
Conclusions Weight loss in morbidly obese patients was associated with a reduction in the prevalence of hepatic fibrosis.

Keywords Liver fibrosis · Cirrhosis · Morbid obesity · Bariatric surgery · Nonalcoholic steatohepatitis

M. Moretto (✉) · C. Kupski · V. D. da Silva · A. V. Padoin · C. C. Mottin
Centro da Obesidade e Síndrome Metabólica do Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Av. Ipiranga 6690/302,
90610-000 Porto Alegre, Brazil
e-mail: mymoretto@hotmail.com

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common hepatic disease in developing countries and the most common cause of chronic hepatic in North America [1]. Although weight loss following bariatric surgery results in a marked improvement in hepatic steatosis [2], the effects of bariatric surgery on hepatic fibrosis are unclear [3]. Since the prognosis of patients with NAFLD is closely related to the development of hepatic fibrosis, it is important to determine the effects of weight loss on hepatic histology, especially on hepatic fibrosis. We have therefore evaluated the prevalence of hepatic fibrosis in morbidly obese patients undergoing bariatric surgery and assessed the correlation between hepatic histology and weight loss.

Materials and Methods

We retrospectively evaluated morbidly obese patients who underwent gastric bypass surgery from 2006 to 2010 at a tertiary care center for the treatment of obesity and metabolic syndrome. Biopsy samples were taken from each patient during surgery and after weight loss.

Liver Biopsies

Liver biopsy samples were taken at the beginning of the surgery using a Trucut 1-mm needle. Biopsy samples obtained following weight loss were obtained percutaneously, with or without ultrasound guidance, using an automatic pistol and 1-mm needles. In some patients, the second biopsy samples were taken during a second surgical procedure with a Trucut 1-mm needle. All

biopsy samples were evaluated by the same pathologist, who was blinded to patient status. We excluded chronic ethanol users (>20 g/day), patients with positive serology for hepatitis B or C, patients with other chronic hepatic diseases, and patients with biopsies evaluated by other laboratories or not suitable for histologic evaluation. Biopsy material was considered insufficient when there were fewer than five portal tracts.

Liver Biopsy Analysis

Hepatic fibrosis was graded from 0 to 4 according to the Brazilian Pathology Society classification [4]: 0 being an absence of fibrosis, 1 being preserved architecture and perisinusoidal fibrosis limited to zone 3, 2 being preserved lobular architecture with perisinusoidal/pericellular fibrosis with sparse thin septum, 3 being altered architecture with septum joining vascular structures and small nodules, and 4 being an architecture with nodules (cirrhosis).

Other Parameters Studied

Demographic and clinical characteristics included patient sex, age, body mass index (BMI), and presence of comorbidities such as type 2 diabetes (T2DM) and dyslipidemia at the times of liver biopsies. Histologic evaluation included grade of steatosis and the presence of ballooning. AST to platelet ratio index (APRI), a serologic marker of fibrosis, was calculated as:

$$\mathrm{APRI} = \mathrm{AST/ULN/Platelets}\left(10^9/\mathrm{L}\right) \times 100.$$

Statistical Analysis

Categorical variables were reported as absolute frequency and percent relative frequency. Quantitative variables were reported as means and standard deviations for symmetric distributions and as medians and interquartile ranges for nonsymmetric distributions. Categorical variables were compared by the chi-square test, with nonindependent categorical variables compared by the McNemar test. Student's t tests were used to compare two sets of quantitative variables in independent samples, and ANOVA was used for three sets of variables. Asymmetrically distributed quantitative variables were compared using the Mann–Whitney, and surgical and postoperative results were compared by the Wilcoxon test. Correlations between asymmetrically distributed quantitative variables were assessed with Spearman's correlation. The level of significance was set at 5%, and 95% confidence intervals were calculated.

Table 1 Relationship of demographic and clinical variables to the presence or absence of fibrosis in surgical biopsy samples

	Hepatic fibrosis		*P*
	Presence *n*=35 (44.9%)	Absence *n*=43 (55.1%)	
Female	23 (65.7)	36 (83.7)	0.115
Age (years)	41.5±12.4	37.9±10.4	0.164
BMI (kg/m^2)	45.6±6.1	45.2±9.4	0.844
T2DM	17 (48.6)	4 (9.3)	<0.001
Dyslipidemia	26 (74.3)	21 (48.8)	0.04
APRI	0.31±0.15	0.30±0.14	0.768
Steatosis			
Mild	2 (5.7)	5 (11.6)	0.366
Moderate	9 (25.7)	15 (34.9)	
Severe	24 (68.6)	23 (53.5)	
Ballooning			
Absence	11 (31.4)	32 (74.4)	<0.001
Grade 1	21 (60)	11 (25.6)	0.004
Grade 2	3 (8.6)	0	0.172

Results

From January 2006 to January 2010, 644 patients underwent gastric bypass surgery. Of these, 85 (13.2 %) were not adequately followed-up, seven died within 1 year of surgery, and 441 (68.5 %) refused or were unable to undergo a second biopsy. Of the 111 patients who underwent a second liver biopsy, 17 were excluded due to poor biopsy material during surgery, 13 were excluded due to poor second biopsy material, and 3 patients were excluded for testing positive for hepatitis (two with hepatitis C and one with hepatitis B).

Of the 78 patients included in this study, 59 (75.6%) were women; average patient age was 39.5±11.4 years, and average presurgical BMI was 45.4±8.1 kg/m^2. Twenty one patients (26.9%) had T2DM before surgery, 47 (60.3%) had dyslipidemia, and 51 (65.4%) had hypertension.

Biopsy samples obtained during surgery showed that 35 patients (44.9%) had fibrosis, and 43 (55.1%) did not. Among the 35 patients with fibrosis, 31 presented with

Table 2 Relationship of surgical to postoperative fibrosis

	Postoperative fibrosis		
Surgical fibrosis	Presence	Absence	Total
Presence	19 (54.3%)	16 (45.7%)	35
Absence	5 (11.6%)	38 (88.4%)	43
Total	24 (30.8%)	54 (69.2%)	78

P=0.027

Table 3 Changes in lobular fibrosis stages after weight loss

Surgical lobular fibrosis	Postoperative lobular fibrosis				
	Absence	Stage 1	Stage 2	Stage 3	Total
Absence	45 (95.7%)	1 (2.1%)	1 (2.1%)	0	47
Stage 1	12 (54.5%)	6 (27.3%)	1 (4.5%)	3 (13.6%)	22
Stage 2	2 (40%)	1 (20%)	2 (40%)	0	5
Stage 3	1 (25%)	0	1 (25%)	2 (50%)	4
Total	60	8	5	5	78

P=0.026

perisinusoidal and/or perivenular (lobular) fibrosis. Four patients had only portal fibrosis, and seven had both lobular and portal fibrosis. Of the 11 patients (14.1 %) with portal fibrosis, seven (9 %) had only a thin septum, two (2.6%) had a portal–portal and/or a vein–portal septum, and two had a septum with nodule formation; the four patients without lobular fibrosis had only a thin septum.

The biopsy samples obtained during surgery showed that all 78 patients had histologic evidence of steatosis, being mild in 7 (9 %), moderate in 24 (30.8 %), and severe in 47 (60.2 %). Thirty five (44.9 %) showed evidence of hepatocellular ballooning.

Since nonalcoholic steatohepatitis (NASH) is diagnosed by the presence of steatosis plus ballooning or fibrosis, some patients with ballooning did not present with fibrosis, and vice-versa. Thus, the total number of patients diagnosed with NASH was 45 (57.7 %). Prior to surgery, the average APRI index, a serologic marker of fibrosis, was 0.29±0.13.

Table 1 shows the variables related to the presence or absence of fibrosis at surgery. We observed no significant differences in gender distribution (P=0.115), age (P=0.164), or BMI (P=0.844) between groups. However, the presence of fibrosis was significantly associated with T2DM (P<0.001) and dyslipidemia (P=0.04). The APRI index was low in both groups and did not differ significantly (P=0.768), nor did steatosis grading (P=0.366). However, a difference was observed in ballooning since 24 of the patients with fibrosis (68.6%) presented with ballooning (P<0.001).

The mean excess weight loss in these 78 patients was 82.4±17.1 %, with an average BMI of 29.3±5.8 kg/m^2 after weight loss. Table 2 shows the relationship between findings of fibrosis at surgery and at second biopsy. After weight loss, 24 patients (30.8%) had fibrosis, including 19 of the 35 patients (54.3%) with fibrosis at surgery.

Of the 43 patients who did not show fibrosis at surgery, five (11.6%) had fibrosis after weight loss.

Table 3 shows the behavior of each grade of lobular fibrosis after weight loss. Of the 22 patients with stage 1 fibrosis, six (27.3%) had stage 1, one (4.5 %) had stage 2, three (13.6%) had stage 3, and 12 (54.5%) had no evidence of fibrosis after weight loss. Of the five patients with stage 2 fibrosis at first biopsy, two (40.0 %) had stage 2, one (20.0 %) had stage 1, and one had no evidence of fibrosis. Of the four patients with stage 3 fibrosis at first biopsy, two (50%) had the same grade, one had a reduced grade, and one had no evidence of fibrosis. Thus, of the 31 patients with lobular fibrosis, 15 (48.4%) had no evidence of fibrosis after weight loss, two (6.5%) had reduced stage, 10 (32.3%) had the same stage, and 4 (12.9%) had an increase in fibrosis stage.

Of the 47 patients who did not present with lobular fibrosis at surgery, 45 (95.7%) did not have fibrosis at the second biopsy, one (2.1 %) had stage 1, and one had stage 2. Table 4 shows the findings in patients with portal fibrosis at the first biopsy. Of the seven patients with portal fibrosis and a thin septum at surgery, four had the same histology, and three did not show this finding after weight loss. Two

Table 4 Changes in portal fibrosis after weight loss

Surgical portal fibrosis	Postoperative portal fibrosis				
	Absence	Thin septum	Portal–portal or vein–portal septum	Septum+initial nodule	Total
Absence	56 (83.6%)	6 (9%)	2 (3%)	3 (4.5%)	67
Thin septum	3 (42.9%)	4 (57.1%)	0	0	7
Portal–portal or vein–portal septum	2 (100%)	0	0	0	2
Septum+initial nodule	0	0	0	2 (100%)	2
Total	61	10	2	5	78

P=0.261

patients with portal–portal and/or portal–vein fibrosis at first biopsy did not show this finding at second biopsy. Two patients with septum and initial nodules at first biopsy had the same histology grade at second biopsy. Thus, of the 11 patients with portal fibrosis at first biopsy, five did not show fibrosis after weight loss, while six showed no change.

Of the 67 patients without portal fibrosis at the first biopsy, 56 (83.6%) showed no change at second biopsy, six (8.9%) had fibrosis with a thin septum, two (3%) had a portal–portal septum, and three (4.5%) had a septum and initial nodules. Thus, 11 patients (16.4%) showed worsened fibrosis after weight loss. Third biopsies were taken from 3 of these 11 patients. In two, taken 14 and 20 months after the second biopsy, histology showed no evidence of lobular or portal fibrosis. In contrast, a biopsy taken from the third patient 16 months after the second biopsy showed no change in stage.

In summary, the prevalence of fibrosis was 44.9% (CI 95% 33.6–56.6%) at the first biopsy and was 30.8% (CI 95% 20.8–42.2%) after weight loss (P=0.027).

We found that the APRI index did not differ significantly in patients with or without total, lobular, or portal fibrosis at first and second biopsies. The mean APRI index in all 78 patients was 0.29±0.13 during surgery and 0.29±0.15 after weight loss (P=0.866).

Biopsies were obtained from 22 patients less than 12 months after surgery; in these patients, the mean excess weight loss was 80.7±16.1% (range 46.0 % to 121.0 %). We observed no difference in excess weight loss between patients from whom the second biopsy was obtained <12 months and >12 months after surgery (P=0.583). Table 5 shows that the presence of fibrosis after weight loss was not associated with patient gender (P=0.345), age (P=0.061), and BMI (P=0.632); with the presence of T2DM (P=0.670) and dyslipidemia (P=0.124); with APRI index (P=0.071); or with steatosis grading (P=0.319). The only difference was related to ballooning since seven patients (29.2%) with fibrosis and three without fibrosis (5.6%) had ballooning (P=0.008). Table 6 shows the presence of ballooning at first and second biopsies. Ballooning was observed in 35 patients (44.9%) during the first biopsy and in 10 (12.8%) during the second biopsy (P<0.001).

After weight loss, due to improvements in fibrosis and ballooning, 21 patients (26.9%) remained with a diagnosis of NASH, compared with 45 (57.7%) at first biopsy.

Table 7 shows the number of portal tracts with or without fibrosis at surgery and at the second biopsy. Patients with fibrosis had a higher number of portal tracts at postoperative than at intraoperative biopsy (12.6±3.0 vs 9.6±3.2, P<0.001).

Table 5 Relationship of demographic and clinical variables to the presence or absence of fibrosis in postoperative biopsy samples

	Fibrosis		P
	Presence n=24 (30.8%)	Absence n=54 (69.2%)	
Female	16 (66.7%)	43 (79.6%)	0.345
Age (years)	43.2±11.2	37.9±11.3	0.061
BMI (kg/m^2)	29.7±3.9	29±6.5	0.632
T2DM	3 (12.5%)	4 (7.4%)	0.670
Dyslipidemia	5 (20.8%)	4 (7.4%)	0.124
APRI	0.34±0.20	0.26±0.12	0.07
Steatosis			
None	4 (16.7%)	8 (14.8%)	0.319
Mild	17 (70.8%)	44 (81.5%)	
Moderate	3 (12.5%)	2 (3.7%)	
Severe	0	0	
Ballooning			
Absence	17 (70.8%)	51 (94.4%)	0.008
Grade 1	7 (29.2%)	3 (5.6%)	
Grade 2	0	0	

Table 6 Relationship of surgical to postoperative ballooning

	Surgical	Postoperative
Absence	43 (55.1%)	68 (87.2%)
Grade 1	32 (41%)	10 (12.8%)
Grade 2	3 (3.9%)	–
Total	78 (100%)	78 (100%)

*P<0.001 for absence versus grade 1

Discussion

The epidemic of obesity has been linked to increases in related diseases such as NAFLD, which may progress to cirrhosis and hepatocelular carcinoma. Hepatic fibrosis

Table 7 Relationship of number of portal tracts to fibrosis

	Number of portal tracts Mean±sd	P
Surgical		
Fibrosis presence	9.7±3.6	0.076
Fibrosis absence	8.3±3.2	
Postoperative		
Fibrosis presence	12.6±3.0	<0.001
Fibrosis absence	9.6±3.2	

plays an important role in the progression to advanced liver disease, and the effects of bariatric surgery on fibrosis outcomes remain unclear [5–7].

Although the prevalence of NASH has been reported higher in males than in females [8, 9], other studies failed to observe this association [10, 11]. We found that fibrosis was more prevalent in males than in females, both at surgical (34.3% vs 16.3%) and postoperative (33.3% vs 20.4%) biopsies, but the differences were not statistically significant.

In morbidly obese patients, the prevalence of steatosis ranges from 95% to 100% and NASH from 20% to 50% [12, 13]. All 78 patients in this study had some degree of steatosis, and 57.7% had NASH, similar to previous observations.

None of the patients of this study had been diagnosed with cirrhosis, although its prevalence in patients undergoing bariatric surgery has been reported to range from 2% to 12% [14–16].

Fibrosis was found in 44.9% of our patients during the first biopsy and was predominantly perisinusoidal or perivenular (lobular), similar to other patients with NASH. Four patients showed only portal fibrosis, without lobular fibrosis, a finding previously observed in morbid obesity related NASH [17–19].

As expected, patients with fibrosis on the first biopsy had a higher prevalence of T2DM than those without fibrosis (48.6% vs 9.3%). Insulin resistance is related to oxidative stress and fibrosis, making T2DM a robust predictor of fibrosis [6, 20, 21]. On the second biopsy, however, the difference (12.5% vs 7.4%) was no longer statistically significant, perhaps due to the reduced number of individuals with T2DM postoperatively. Alternatively, even if these patients still had diabetes, their serologic insulin concentrations were lower than preoperative, reducing their insulin resistance.

Ballooning is a feature of major importance in NASH as its presence has been associated in prognostic studies with more aggressive disease and a higher incidence of cirrhosis. [17, 18] At surgical biopsy, 68.6% of our patients with fibrosis and 25.6% of patients without fibrosis presented with ballooning. After weight loss, these percentages had decreased to 44.9% and 12.8%, respectively, decreases probably related to the prevalence of fibrosis.

Of the 35 patients with fibrosis (lobular and portal) at first biopsy, 16 (45.7%) did not have fibrosis at the second biopsy, while 19 (54.3%) did. Of the 43 patients without fibrosis at first biopsy, 38 (88.4%) remained without fibrosis at second biopsy, while 5 (11.6%) had developed fibrosis after weight loss.

A Cochrane Database Review analysis in 2010 [3] of 21 studies of histological hepatic outcomes yielded findings similar to ours. Although weight loss was associated with worsened fibrosis in some patients, it was mostly associated with improvements or no change.

Although hepatic biopsy is the standard method for studying hepatic fibrosis, it has limitations. It is an invasive method, obtaining a small fragment of hepatic tissue that may not be representative of the entire liver. Moreover, there are also possibilities of inter- and intraobserver errors. We found that patients with postoperative fibrosis had a greater number of portal tracts than those without fibrosis, and larger sized samples are more likely to show some alterations, suggesting that fibrosis may have been associated with sample size. In addition, we may have underestimated the number of patients without fibrosis.

Although not all of our patients showed improvements in fibrosis, there was a decrease in fibrosis in a majority of patients, as well as reductions in steatosis and ballooning, all known routes for the development of cirrhosis and hepatocellular carcinoma from NAFLD.

Conflict of Interest None of the authors has any conflicts of interest to declare.

Disclosure No external funding supported this work. None of the authors has any financial interest to declare.

References

1. Greenfield V, Cheung O, Sanyal AJ. Recent advances in nonalcoholic fatty liver disease. Curr Opin Gastroenterol. 2008;24:320–7.
2. Mottin CC, Moretto M, Padoin AV, et al. Histological behavior of hepatic steatosis in morbidly obese patients after weight loss induced by bariatric surgery. Obes Surg. 2005;15:788–93.
3. Chavez-Tapia NC, Tellez-Avila FI, Barrientos-Gutierrez T, Mendez-Sanchez N, Lizardi-Cervera J, Uribe M. Bariatric surgery for non-alcoholic steatohepatitis in obese patients. Cochrane Database Syst Rev 2010: CD007340.
4. Freitas LAR, Cotrim HP. Atlas histológico. Esteato-Hepatite Não Alcoólica. 2006.
5. Farrell GC, George J. Overview: an introduction to NASH and related fatty liver disorders. In: Farrell GC, Hall P, George J, McCullough AJ, editors. Fatty liver disease: NASH and related disorders. Malden: Blackwell; 2005.
6. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. Hepatology. 2003;37:1202–19.
7. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology. 2010;51:1820–32.
8. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology. 2001;121:91–100.
9. Ong JP, Elariny H, Collantes R, et al. Predictors of nonalcoholic steatohepatitis and advanced fibrosis in morbidly obese patients. Obes Surg. 2005;15:310–5.

10. Spaulding L, Trainer T, Janiec D. Prevalence of non-alcoholic steatohepatitis in morbidly obese subjects undergoing gastric bypass. Obes Surg. 2003;13:347–9.
11. Beymer C, Kowdley KV, Larson A, Edmonson P, Dellinger EP, Flum DR. Prevalence and predictors of asymptomatic liver disease in patients undergoing gastric bypass surgery. Arch Surg. 2003;138:1240–4.
12. Oliveira CPMS, Couto CA. Doença hepática gordurosa não alcoólica e esteato-hepatite não alcoólica. In: Mattos, A.A., Dantas-Corrêa, E.B.(eds.) Tratado de hepatologia. 2010; Editora Rubio: Rio de Janeiro.
13. Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2008;6:1396–402.
14. Kral JG, Thung SN, Biron S, et al. Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. Surgery. 2004;135:48–58.
15. de Freitas AC, Campos AC, Coelho JC. The impact of bariatric surgery on nonalcoholic fatty liver disease. Curr Opin Clin Nutr Metab Care. 2008;11:267–74.
16. Clark JM. The epidemiology of nonalcoholic fatty liver disease in adults. J Clin Gastroenterol. 2006;40 Suppl 1:S5–10.
17. Brunt EM, Tiniakos DG. Histopathology of nonalcoholic fatty liver disease. World J Gastroenterol. 2010;16:5286–96.
18. Mello ES, Alves VAF. Atlas de patologia hepática. São Paulo: Editora Manole; 2010.
19. Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. J Hepatol. 2006;45:600–6.
20. McCullough AJ. The epidemiology and risk factors of NASH. In: Farrell GC, Hall P, George J, McCullough AJ, editors. Fatty liver disease: NASH and related disorders. Malden: Blackwell; 2005.
21. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology. 1999;30:1356–62.