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Histological Behavior of Hepatic Steatosis in Morbidly Obese Patients after Weight Loss Induced by Bariatric Surgery

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Background: Hepatic steatosis has a high prevalence among morbidly obese patients. Its relation to steatohepatitis and cirrhosis has been extensively studied among these patients. The aim of this study was to evaluate the behavior of hepatic steatosis with weight loss 1 year after bariatric surgery.

Methods: This study is a historical cohort that compared liver biopsies obtained from morbidly obese patients during the bariatric operation, with percutaneous biopsies taken from the same patient 1 year after surgery. The results were compared with weight loss, patients' profile (gender, age, body mass index (BMI) and waist/hip ratio), and with the presence of co-morbidities such as diabetes, hypertension, and dyslipidemia.

Results: 90 patients who had liver biopsies taken at the operation and postoperative period for bariatric surgery were included. The prevalence of hepatic steatosis was 87.6%. The average percent of excess weight loss was 81.4%. On the second biopsy, 16 patients (17.8%) of the total had the same degree of steatosis, 25 (27.8%) improved their steatosis pattern and 49 (54.4%) had normal hepatic tissue. There was no statistical difference regarding age, BMI, waist/hip ratio, and co-morbidities (*P*>0.05), but there was a difference in gender (*P*=0.044).

Conclusion: Significant improvement in the hepatic histology of steatosis was observed after weight loss induced by bariatric surgery in most patients. There was no patient with a worsening in the histology.

Key words: Hepatic steatosis, morbid obesity, bariatric surgery

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Introduction

Nonalcoholic fatty liver disease (NAFLD) represents a wide spectrum of conditions characterized histologically mainly by macrovesicular hepatic steatosis, and occurs in patients who do not consume alcohol in amounts considered to be harmful to the liver.[1] The histological findings of liver damage range from simple steatosis to nonalcoholic steatohepatitis (NASH) to advanced fibrosis and cirrhosis.[2-4]

Hepatic steatosis has been associated with several conditions, among them morbid obesity,[5-7] which is considered an independent risk factor for the occurrence of liver damage and could contribute to liver fibrosis.[8] There is increasing evidence that NAFLD often represents the hepatic component of the metabolic syndrome, characterized by obesity, hyperinsulinemia, peripheral insulin resistence, diabetes, hypertriglyceridemia and hypertension.[1,9]

Although not common, the progression to cirrhosis in mild NAFLD has been described,[10,11] and any amount of fat is thought to sensitize the liver to injury from other causes.[12]

The severity of steatosis seems to play an important role in the development of fibrosis and progression of liver damage.[13] Steatohepatitis is now regarded as an important cause of end-stage liver disease and may also be the cause of an unknown number of cases of cryptogenic cirrhosis. Interestingly, 1.4 % of morbidly obese patients submitted to antiobesity surgery are found to have cirrhosis.[14] Unfortunately, once cirrhosis is established, the only treatment available for

advanced disease is orthotopic liver transplantation.[15] However, some improvement of cirrhosis has been reported in operated patients who have lost weight.[16]

Therapy for NASH remains empirical and limited to treating conditions associated with it, such as diabetes mellitus, obesity, and hyperlipidemia, as well as avoidance of hepatotoxic pharmacological agents. Weight loss is considered a treatment for NASH and steatosis, and bariatric surgery is currently considered the only method that provides sustained and substantial weight loss for most severely obese patients.[16] The aim of this study was to evaluate the behavior of hepatic steatosis with weight loss, 1 year after bariatric surgery.

Methods

A historical cohort study of patients submitted to open Roux-en-Y gastric bypass (RYGBP) by the Fobi technique,[17] was carried out at Centro da Obesidade Mórbida do Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Brazil. The liver biopsy was chosen to assess liver histology and its alterations, because liver biopsy is considered as the gold standard.[18] Liver biopsy has been performed routinely during the operation of all patients submitted to bariatric surgery by our group, and all samples were analyzed by the pathology laboratory of São Lucas Hospital, PUCRS. The anatomical pathology classification used for steatosis took into consideration the amount of hepatic parenchyma involved (mild, <1/3; moderate, 1/3 - 2/3, and severe, >2/3).[19]

Patients are always informed about the prevalence of steatosis among morbidly obese subjects, its clinical relevance, as well as the need to keep it under control in order to avoid future damage to the liver.[20] All patients receive a free and descriptive informed consent, including a list of postsurgical routine tests. A postsurgical hepatic biopsy is listed among such tests, and is performed in case histological alterations of the liver are detected (see below). A permission allowing the use of anonymous data for research purposes is also part of this form.

The anatomical pathology report of the hepatic tissue is discussed with each patient postoperatively. In cases where steatosis is detected, a percutaneous biopsy is recommended 1 year after the bariatric surgery, because this is the usual time in which most of the patients have their most significant weight loss.

The selected subjects in this study underwent the RYGBP from July 2001 to June 2003. All patients had a diagnosis of steatosis in the operative biopsy, and had a percutaneous liver biopsy 1 year after the operation. The operative biopsies consisted of a wedge biopsy until August 2002; from then on, the tissue was obtained by needle biopsy. The liver biopsies obtained 1 year after the surgery were taken by percutaneous needle biopsy (Bard Magnum biopsy needles), and performed by the same physcian (CK). The 1-year percutaneous needle biopsy was performed at the day hospital unit, always in the morning, with a recovery and observation time of 5 hours; there was no complication associated with the biopsy.

Patients were excluded from this study if there were no histological alterations on the intraoperative biopsy. Other exclusion criteria was the presence of a histological alteration other than steatosis, history of ethanol abuse or other possible etiology for the hepatic damage (viral hepatitis, autoimmune hepatitis, hemochromatosis), and also patients with insufficient material at the biopsy.

Patients were considered *cured* from steatosis when the second biopsy showed normal hepatic parenchyma. They were considered *improved* in those cases in which the degree of steatosis had diminished, and *unaltered* in those in which the histological pattern remained the same.

The weight loss was calculated percentually, in terms of excess of weight lost based on the BMI 25 kg/m^2.[21]

Patients with fasting glucose ≥126 mg/dl measured at least twice, or patients whose oral glucose tolerance tests (75 g of glucose) showed impaired results (>200 mg in 2 hours) were considered diabetic (DM), as were those with a previous diagnosis of diabetes on pharmacological treatment.

Patients who were being treated with anti-hypertensive agents, independent of whether they were stabilized or not, and/or subjects with values of systemic arterial pressure ≥140/90 mmHg, were considered hypertensive.

Subjects with a total cholesterol ≥200 mg/dl, triglycerides ≥150 mg/dl or HDL-cholesterol <40 mg/dl for the male and <35 for the female or LDL-cholesterol ≥130 mg/dl were considered dyslipi-

demic. Those who were being treated with oral hypolipemiants were also considered dyslipidemic.

The collected data from operated subjects by this group was systematically recorded in a database. Qualitative variables were compared through Chi-square test on contingency tables. The steatosis degrees observed during the intraoperative and 1-year postoperative biopsies were divided in three categories (mild, moderate and severe). The differences observed were analyzed through the Wilcoxon test to verify the significance between the two time periods. The quantitative variables were analyzed with the ANOVA statistical test. For all statistical analyses, a difference was considered significant when $P \leq 0.05$.

This study was revised and approved by the *Comitê de Ética e Pesquisa** at the Pontifícia Universidade Católica do Rio Grande do Sul, Brazil.

Results

From July 2001 to June 2003, 186 morbidly obese patients underwent RYGBP by the same surgical team. The prevalence of histological alteration for these patients was 91.39%. The most frequent diagnosis was hepatic steatosis, found in 163 cases (87.63%). Four patients (2.15%) presented steatohepatitis in the first biopsy, two (1.07%) had cirrhosis, and one (0.53%) had severe chronic hepatitis. Only 16 patients (8.60%) had a normal hepatic tissue (Table 1).

Considering the 163 patients with hepatic steatosis, 51 were classified as having mild steatosis (31.29%), 43 had moderate steatosis (26.38%), and 69 patients had severe steatosis (42.33%). Fifty-four had regular follow-up with the surgical team, but refused to undergo hepatic biopsy; 15 lacked proper postoperative follow-up, making the hepatic biopsy impossible; and one patient died from complications during the immediate postoperative period.

From the initial 163 patients, 93 had a percutaneous biopsy performed 1 year after bariatric surgery, but three cases were considered as having insufficient liver tissue for anatomical pathology analysis.

The 90 eligible patients had a mean age of 35.6 years (± 1.10), initial BMI of 46.7 (± 0.88) and had a mean excess weight loss of 81.4 % (± 1.95) at 1 year.

*Research and Ethics Committee

Table 1. Liver histology at bariatric surgery

Anatomical Pathology Report	N	(%)
Normal hepatic tissue	16	(8.60)
Hepatic steatosis	163	(87.63)
Mild	51	
Moderate	43	
Severe	69	
Steatohepatitis	4	(2.15)
Cirrhosis	2	(1.07)
Severe chronic hepatitis	1	(0.53)
Total hepatic abnormalities	170	(91.39)
Total	186	

The first 49 operative biopsies were performed as a tissue wedge and the last 41 were obtained through a needle. No differences in terms of patient profile and degree of steatosis for those who had the two methods of intraoperative biopsy were observed ($P>0.05$). These 90 patients had their first histology result classified as mild steatosis in 27 (30%), moderate in 24 (26.7%) and severe in 39 (43.3%). Such distribution was the same when considering the patients who had performed only the first biopsy ($P=0.968$).

Considering the percutaneous biopsy obtained 1 year after bariatric surgery, 49 patients (54.4%) showed normal hepatic tissue, 34 (37.8%) showed mild steatosis, 4 (4.4%) moderate and 3 (3.3%) severe (Table 2). Such difference was considered significant by the Wilcoxon test, z = -7.593 was observed, $P<0.0001$.

Analyzing the patients' histological modification 1 year after surgery and weight loss, we consider that 49 (54.4%) were cured (without steatosis), 25 (27.8%) improved their histological pattern, 16 (17.8%) remained unaltered, and none had a worse liver condition (Table 2).

Complete healing was observed in 59.3% of patients with mild steatosis, 62.5% in patients with moderate steatosis and 46.1% in patients with severe steatosis. Improvement in the degree of steatosis was observed in 29.2% of patients with moderate steatosis changing to mild steatosis, and 46.2% of patients with severe steatosis had the severity of steatosis reduced. Among the patients who did not improve the degree of steatosis, 40.7% had mild steatosis, 8.3% had moderate steatosis and 7.7% had severe steatosis in the first biopsy (Table 2).

The characteristics of the patients who showed an

Table 2. Steatosis before and after weight loss

Degree of Steatosis	At bariatric surgery	At 1 year after bariatric surgery			
		Absent	Mild	Moderate	Severe
Mild	27 (30.0%)	16 (59.3%)	11 (40.7%)	-	-
Moderate	24 (26.7%)	15 (62.5%)	7 (29.2%)	2 (8.3%)	-
Severe	39 (43.3%)	18 (46.2%)	16 (41%)	2 (5.1%)	3 (7.7%)
Total	90 (100%)	49 (54.4%)	34 (37.8%)	4 (4.4%)	3 (3.3%)

Wilcoxon, z = -7.593, $P<0.0001$

improvement in the classification of steatosis is shown in Table 3. There is no significant difference regarding age, BMI, waist/hip ratio, presence of DM, hypertension and dyslipidemia ($P>0.05$). The only significant difference observed was the patients' gender ($P=0.044$).

To verify a possible association between gender and other variables of the patients' characteristics they were categorized according to gender. Female patients showed a mean waist / hip ratio of 0.89 ± 0.013, significantly lower than males (1.02 ±0.020), $P<0.0001$. No significant difference was observed regarding age or BMI, for both males and females ($P>0.05$). Also, no significant difference was found considering the presence of co-morbidities (DM, hypertension, and dyslipidemia), or the kind of biopsy performed ($P>0.05$).

The mean excess weight loss (EWL) observed for all 90 patients was 81.4% (± 1.95). The mean EWL observed for the patients without improvement in the steatosis classification was 72.5% (± 5.89). This EWL reached 78.0% (± 3.37) among those who improved their classification, and 85.9% (± 2.33) among those who reached complete healing, a significant difference ($P=0.022$) (Figure 1).

Discussion

Because there is no specific treatment currently available for hepatic steatosis, treatment attempts are mostly limited to treating its causes. Obesity is a well-known cause of steatosis, being even more important in morbid obesity, where a very high prevalence of steatosis is found.[7,8,18,20,22,23] Accordingly, this study has found that 87.6% of morbidly obese patients present steatosis. It was expected that weight loss could produce favorable effects on steatosis. Because the gold standard for diagnosis of steatosis is tissue examination,[24] biopsy was performed to demonstrate whether steatosis regression can occur as a result of weight loss after bariatric surgery.

Some authors[22,25] have reported improvements in

Table 3. Patients' profile and histology after weight loss

	Unaltered Steatosis N = 16	Improved Steatosis N = 25	Cured (No Steatosis) N = 49	Total N = 90	*P*
Age (years)	37.56 (±2.62)	38.80 (±2.05)	33.29 (±1.44)	35.58 (±1.11)	0.067
BMI (kg/m^2)	49.08 (±3.00)	46.92 (±1.56)	45.82 (±1.03)	46.71 (±0.88)	0.402
Waist / Hip	0.91 (±0.032)	0.97 (±0.028)	0.91 (±0.016)	0.93 (±0.0130)	0.246
Male Subjects	3 (18.8%)	12 (48.0%)	11 (22.4%)	26 (28.9%)	0.044
Female Subjects	13 (81.3%)	13 (52.0%)	38 (77.6%)	64 (71.1%)	0.044
Diabetes	0	4 (16.0%)	5 (10.2%)	9 (10%)	0.249
Hypertension	8 (50.0%)	16 (64.0%)	23 (46.9%)	47 (52.2%)	0.373
Dyslipidemia	10 (62.5%)	18 (72.0%)	38 (77.6%)	66 (73.3%)	0.490

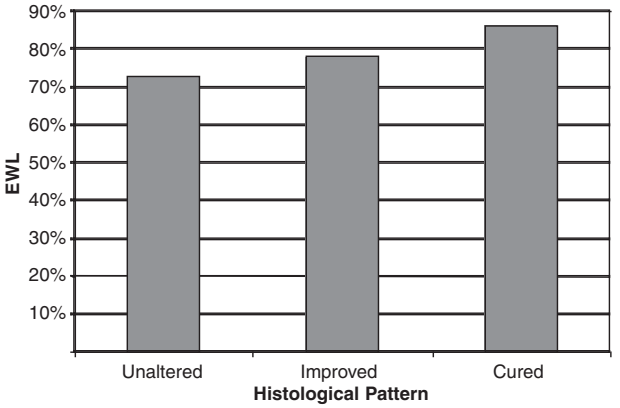

Figure 1. Percent excess weight loss (EWL) and changes in histological pattern 1 year after bariatric surgery (F=4.007, *P*=0.022).

steatosis after bariatric surgery. However, these studies included patients in whom a second hepatic biopsy was performed because a second surgery was required, in different postoperative time periods, and not systematically as was done in this study.

The most important finding of this study was that 54.4% of morbidly obese patients with steatosis during the bariatric operation showed normal hepatic histology after weight loss, and 27.8% had improvement in their degree of steatosis. In other words, after weight loss, only 17.8% of morbidly obese patients did not show improvement (unaltered histology), and none had their condition aggravated.

One of the main factors relating NASH with fibrosis is the severity of steatosis,[13] and our patients have shown an important improvement in the prevalence of severe steatosis, 39 (43.3%) vs 3 (3.3%). Patients with higher percentages of excess weight loss had more marked improvement in their degree of steatosis. We could not find another factor, besides marked weight loss, that could be considered important for the improvement in steatosis. Although a difference in terms of gender was observed in the liver histology after weight loss, no clear reason for this finding was found.

In conclusion, there was a significant improvement in the histological behavior of steatosis induced by weight loss after bariatric surgery, reinforcing the therapeutic importance of bariatric surgery. Further monitoring of the hepatic parenchyma status, with more patients and a longer follow-up is warranted, in order to confirm and extend the findings of this study.

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