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Changes in Liver Histology Accompanying Massive Weight Loss after Gastroplasty for Morbid Obesity

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Background: Nonalcoholic steatohepatitis (NASH) is common in morbid obesity. Our goal was to evaluate the alterations in liver histology and biochemistry before and after weight loss in 51 morbidly obese patients following Mason's vertical banded gastroplasty.

Methods: Two biopsies were performed (on entry and after an average of 18 months), while 16 of these subjects had a third biopsy 17 months after the second.

Results: On entry, steatosis and steatohepatitis (mostly grade 3) were present in 98.0% and fibrosis (mostly stage 2) in 94.1% of the subjects. After an excess weight loss of 66%, steatosis and steatohepatitis improved significantly (P<0.001). Although a significant overall decrease in fibrosis occurred (P=0.002), 21 patients (41.1%) did not change and only 6 patients (11.7%) increased in fibrosis. None developed cirrhosis. The decrease in steatohepatitis was significantly correlated (P=0.011) with the reduction of BMI. Fasting serum glucose, lipids, lipoproteins, transaminases, gamma-glutamyl transpeptidase, alkaline phosphatase and fibrinogen were also significantly improved at the time of the second biopsy. The third biopsy performed in 16 of the subjects showed further significant improvement in liver histology.

Conclusion: NASH improved significantly with massive weight loss in non-diabetic, non-alcoholic, morbidly obese subjects, while fibrosis improved in nearly half of the patients.

Key words: Liver biopsy, nonalcoholic steatohepatitis, fibrosis, morbid obesity, weight loss, surgery, gastroplasty

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Introduction

Nonalcoholic fatty liver is the most common liver disease worldwide; its histologic spectrum ranges from fatty liver to nonalcoholic steatohepatitis (NASH).[1] This pattern has been found to accompany obesity, diabetes, hyperlipidemia, protein malnutrition, jejunoileal bypass, intravenous hyperalimentation and the use of hepatotoxic drugs, or may be idiopathic.[1-2] In morbid obesity, fatty change ranges from a centrilobular (Zone 3) distribution (when mild to moderate) to a diffuse infiltration (when marked).[2] Large-droplet fatty change of the liver is common in asymptomatic obese individuals (the incidence in a large series of biopsies from obese subjects is 60% to 100%)[2-5] and is considered a benign, nonprogressive disease.[6] However, it has become evident that some morbidly obese patients develop severe NASH showing all the features of alcoholic hepatitis with macrovesicular fat, lobular and portal inflammation, Mallory bodies and eventually progression to fibrosis and even cirrhosis. Whereas there is accumulating data that obesity is an independent risk factor for more advanced fibrosis in patients with fatty liver,[7] the role of weight loss is uncertain.[8]

This study was designed to assess the importance of obesity-related liver disease and the effect of weight loss on liver histology and biochemistry. Because there is a large discrepancy between the

medical history and laboratory findings on the one hand, and the histological picture on the other,[9,10] we used liver biopsy to detect progression to more advanced liver disease in the morbidly obese patient.

Materials and Methods

Among 216 morbidly obese patients with a body mass index (BMI) >40 who underwent Mason's vertical banded gastroplasty (VBG)[11] for weight reduction in our Department from November 1998 to October 2001, 51 non-diabetic, non-alcoholic, subjects (33 females and 18 males) were included in this study. To be eligible for the study, patients had to fulfill the following criteria: 1) no type 2 diabetes mellitus; 2) no excess drinking as defined by an average daily consumption of alcohol >20 g for women and >30 g for men; 3) no evidence of drug-induced liver disease on liver biopsy, no total parenteral nutrition and no administration of known hepatotoxic medication; 4) negative testing for hepatitis B and C; 5) negative testing for antinuclear, anti-smooth muscle actin, anti-liver-kidney microsome and anti-mitochondrial antibodies; 6) exclusion of other liver diseases (alcoholic liver disease, viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson's disease, alpha-l-antitrypsin deficiency); and 7) no history or finding consistent with another specific liver disease, heart failure, organic renal disease, cancer or other major disease.

Indications for surgery included presentation of morbid obesity, at least two dietary trials of weight reduction under direction of physicians or dietitians and/or associated co-morbid conditions. After VBG, all patients were put on a special liquid diet. Daily intake was 655 calories (61.4 g protein, 91.2 g carbohydrates, 4.9 g fat) and vitamins and minerals in normal daily requirements. These were distributed in five meals. The ingestion of only 50 ml/meal was necessary due to the small volume of the gastric pouch. After 3 months, patients were gradually put on a regular diet.

A wedge liver biopsy was taken as a routine at the beginning of the surgical procedure from the edge of right lobe of the liver. The tissue was immediately fixed in 10% buffered formalin solution and sent to the histopathology laboratory for routine pathologic examination. Paraffin-embedded tissue blocks were sectioned at 4 to 6 microns. Histological sections were stained with hematoxylin and eosin and with periodic acid-Schiff before and after diastase digestion for the necroinflammatory grading. The Chromotrope Aniline Blue trichrome and Sweet's reticulin stains were reviewed for fibrosis and architectural changes.

All repeat postoperative percutaneous liver biopsy specimens were obtained with a 14-gauge biopsy needle (Medical Device Technologies Inc., Gainesville, FL, USA).

A single hepatopathologist (CS), blinded to the clinical and laboratory data, examined all tissue sections, assessed liver histology using a systemic approach of necroinflammatory grading and fibrosis staging as described by Brunt et al.[12] Liver biopsy specimens were included if there were six or more portal tracts; none were excluded for being inadequate.

Macrovesicular steatosis was scored on a scale of 0 to 3 based on percent of hepatocytes in the biopsy involved (0 is none; 1 is up to 33%; 2 is 33-66%, 3 is >66%). Liver Fibrosis (F) was assessed on a scale of 0 to 4 (Stage F0, fibrosis absent; Stage F1, zone 3 perisinusoidal/pericellular fibrosis focally or extensively present; Stage F2, zone 3 perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis; Stage F3, perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis; Stage F4, cirrhosis). The proposal for assigning activity grading for steatohepatitis is shown in Table 1. Regeneration was assessed by the thickness of the liver plates amounting to twin or three cells thick.

Written informed consent was obtained from all patients, and the study was conducted in conformance with the Helsinki Declaration. Permission for the study was obtained from "Evagelismos" Hospital Ethics Committee.

Statistical Methods

The data are presented as Mean ± Standard Error of the Mean or by the median and range for skewed continuous variables, and by the frequency distribution for categorical variables. The normality assumption was tested by the Kolmogorov-Smirnov test and the paired sample *t*-test as appropriate. In cases where the normality assumption was violated and for ordinal variables, the non-parametric Wilcoxon signed rank

Table 1. Necroinflammatory Grading System for Steatohepatitis[12]

Mild, grade 1: Steatosis (predominantly macrovesicular) involving up to 66% of biopsy; may see occasional ballooned zone 3 hepatocytes; scattered rate intra-acinar polymorphonuclear leukocytes ± intra-acinar lymphocytes; no or mild portal chronic inflammation.

Moderate, grade 2: Steatosis of any degree; ballooning of hepatocytes (predominantly zone 3) obvious; intra-acinar polymorphonuclear leukocytes noted, may be associated with zone 3 pericellular fibrosis; portal and intra-acinar chronic inflammation noted, mild to moderate.

Severe, grade 3: Para-acinar steatosis; ballooning and disarray obvious, predominantly in zone 3; intra-acinar inflammation noted as scattered polymorphonuclear leukocytes, polymorphonuclear leukocytes associated with ballooning of hepatocytes ± mild chronic inflammation; portal chronic inflammation mild or moderate, not marked.

test was used. Correlations were calculated using the Spearman rank correlation coefficient.

A further statistical analysis was performed for the subgroup of the 16 patients that underwent a third liver biopsy. For continuous and ordinal categorical variables, comparisons were performed by the non-parametric Friedman test. In the case where a significant difference was found, paired comparisons were further made by the Wilcoxon signed rank test.

Results

At the first liver biopsy, body weight ranged from 103 to 207 kg (mean 150.9±4 kg; this was 79-296% above the ideal weight of the patients) and the BMI ranged from 40 to 84 kg/m^2 (mean 52.8±1 kg/m^2). Overall excess weight loss after surgery was 66% within 6 to 35 months (P<0.001).

Changes in blood chemistry values before and after weight reduction are given in Table 2.

Histopathology

Steatosis and steatohepatitis were present in 98.0% of the subjects, with the majority having grade 3. Fibrosis was found in 94.1% of the subjects, with the majority having stage F2. Cirrhosis was not detected in any of the biopsies.

At follow-up second liver biopsy, hepatic steatosis and steatohepatitis were absent in 17.6% of the subjects, while the majority had grade 1 steatosis and steatohepatitis. Fibrosis was absent in 13.7% of the subjects, with the majority having stage F1. These second postoperative percutaneous liver biopsy specimens were obtained at 18±9.6 months after gastroplasty.

Changes in liver histological findings from the first to the second biopsy are given in Table 3. A significant improvement was noted regarding steatosis, steatohepatitis, lipogranulomas (P<0.001) and fibrosis (P=0.002). Regenerative activity was markedly increased, but did not reach statistical significance (P=0.053). The numbers of patients who improved, remained the same, or had worsening of the histological features on the second biopsy are shown in Table 4.

A subgroup of 16 patients (12 females and four males) that continued to lose weight, agreed to have a third liver needle biopsy at 17±6 months after the second biopsy. Additional mean excess weight loss was 10.9% (P<0.001). These 16 subjects had further significant reduction of liver steatosis (P=0.014), steatohepatitis (P=0.011) and fibrosis (P=0.008). Accompanying these changes, significant further decreases in fasting serum glucose (P=0.028), AST (P=0.038), alkaline phosphatase (P=0.034), triglycerides (P=0.014) and LDL cholesterol (P=0.011) levels were observed.

Correlations

Analysis of the association between clinical characteristics, changes in histological features and the changes in laboratory data, as well as intercorrelations between changes in histological features, are shown in Table 5.

Discussion

Obesity today is a big threat to public health. Worldwide, 1.7 billion adults and >22 million children are obese.[13] Although fatty liver of non-alcohol origin is considered a benign disease,[10,14] obese patients with NASH may develop progressive liver disease leading to cirrhosis and liver-related death.[5,15,16]

In several studies, 24% to 95% of the obese

Table 2. Laboratory characteristics of the subjects before and after massive weight loss (1st vs 2nd biopsy)

	1st biopsy (mean±SEM)	2nd biopsy (mean±SEM)	*P*-value
Fasting plasma glucose (normal 60-110 mg/dl)	94.8±1.6	86.9±1.0	**<0.001**
AST (normal 5-40 UI/l)	27.7±2.1	19.3±1.2	**0.001**
	median=24	median=17	**<0.001***
	min-max:11-79	min-max:10-53	
ALT (normal 5-45 UI/l)	39.8±4.3	20.3±2.3	**<0.001**
	median=32	median=16	**<0.001***
	min-max:9-154	min-max:6-115	
Alkaline phospatase (normal 35-150 UI/l)	79.8±3.4	73.2±5.8	0.224
	median=73	median=65	**0.013***
	min-max:49-182	min-max:11-219	
γ-GT (normal 11-50 UI/l)	21.5±3.5	18.0±3.4	0.130
	median=16	median=13	**0.008***
	min-max:4-171	min-max:1-141	
Bilirubin total (normal 0.3-1.1 mg/dl)	0.79±0.03	0.76±0.04	0.555
	median=0.74	median=0.70	0.362*
	min-max:0.35-1.60	min-max:0.23-1.60	
Total cholesterol (normal 130-200 mg/dl)	205.5±7.0	181.0±6.5	**0.001**
Triglycerides (normal 40-150 mg/dl)	154.6±12.1	107.3±7.2	**<0.001**
	median=136	median=96	**<0.001***
	min-max:46-506	min-max:30-256	
HDL cholesterol (normal 30-80 mg/dl)	31.1±1.2	36.8±1.8	**0.003**
	median=29	median=35	**0.002***
	min-max:15-59	min-max:17.6-78	
LDL cholesterol (normal 60-180 mg/dl)	144.9±6.3	121.5±5.3	**<0.001**
Protein (normal 6.2-8.5 g/dl)	7.22±0.07	7.14±0.08	0.391
Albumin (normal 3.5-5.5 g/dl)	4.16±0.04	4.18±0.07	0.804
Globulins (normal 2.5-3.3 g/dl)	3.06±0.05	2.98±0.07	0.225
Fibrinogen (normal 200-400 mg/dl)	377.7±13.7	353.5±15.5	0.168
	median=362	median=342	**0.042***
	min-max:230-580	min-max:174-709	
INR (normal 0.8-1.2)	1.05±0.01	1.07±0.01	0.082
	median=1.00	median=1.05	0.121*
	min-max:1.00-1.29	min-max:1.00-1.39	

Paired samples *t*-test, *Wilcoxon signed rank test. Bold = significant. SEM = Standard Error of the Mean.

patients had NASH.[5,10,17-21] The prevalence of liver fibrosis ranged from 6% to 74%[2,5,10,17-21] and that of cirrhosis from 0% to 24%.[2,5,10,17-21] In our series, 98% and 94% of the subjects had NASH and fibrosis respectively, while cirrhosis was not established. Our analysis showed a significant regression of steatosis and steatohepatitis with weight reduction. In this study, the majority (more than 84%) of subjects that had paired liver biopsies, had improvement in steatosis or steatohepatitis grade. No patient had progression in severity of steatosis or steatohepatitis.

There was also a significant overall decrease in severity of fibrosis and lipogranulomas. It is noteworthy that liver fibrosis was unchanged in 21 patients (41.1%) and progressed only in six patients (11.7%), although none of these subjects progressed to cirrhosis. That means that the fibrosis stage improved in less than half of the subjects (47%). Consistent with that finding is the observation that regeneration got better in only 39% of the patients. Similarly, improvement of lipogranulomatous changes was found in half of the subjects (49%).

The high prevalence of NASH and fibrosis in our study population may be due to their mean superobese state (mean BMI 52.8). The high incidence of fibrosis on entry biopsy may also in part be explained by the fact that the amount of liver fibrosis in wedge biopsies is always higher than that seen

Table 3. Liver histology before and after massive weight loss induced by gastroplasty (1st vs 2nd biopsy)

	1st biopsy (%)	2nd biopsy (%)	*P*-value
Steatosis			
0	1 (1.97)	9 (17.6)	
1	11 (21.6)	36 (70.6)	
2	15 (29.4)	6 (11.8)	
3	24 (47.1)	0 (0.0)	**<0.001**
Steatohepatitis			
0	1 (1.97)	9 (17.6)	
1	11 (21.6)	35 (68.6)	
2	16 (31.4)	7 (13.7)	
3	23 (45.1)	0 (0.0)	**<0.001**
Fibrosis			
0	3 (5.9)	7 (13.7)	
1	17 (33.3)	25 (49.0)	
2	23 (45.1)	14 (27.5)	
3	8 (15.7)	5 (9.8)	
4	0 (0.0)	0 (0.0)	**0.002**
Lipogranulomas			
0	22 (43.1)	39 (76.5)	
1	9 (17.6)	9 (17.6)	
2	13 (25.5)	3 (5.9)	
3	7 (13.7)	0 (0.0)	**<0.001**
Regeneration			
0	30 (58.8)	14 (27.5)	
1	11 (21.6)	23 (45.1)	
2	6 (11.8)	13 (25.5)	
3	4 (7.8)	1 (1.97)	0.053

Wilcoxon signed rank test. Bold = significant.

Table 4. Number of patients who improved, remained the same or deteriorated after massive weight loss (1st vs 2nd biopsy)

	Patients who improved No. (%)	Stable patients No. (%)	Patients who deteriorated No. (%)
Steatosis	43 (84.3%)	8 (15.6%)	0 (0%)
Steatohepatitis	44 (86.2%)	7 (13.7%)	0 (0%)
Fibrosis	24 (47.0%)	21 (41.1%)	6 (11.7%)
Lipogranulomas	25 (49.0%)	23 (45.0%)	3 (5.8%)
Regeneration	20 (39.2%)	25 (49.0%)	6 (11.7%)

in percutaneous biopsies obtained in a deeper site. Taking this fact into account, we have estimated fibrosis in our study not on the basis of subcapsular fibrosis but on the observation of the existence of portal-to-portal fibrosis as well as perisinusoidal / pericellular fibrosis. Although initial biopsies may be biased towards overestimation of fibrosis, we believe that our series of liver biopsies indeed describes an overall decrease in fibrosis because this trend continued in the third biopsy.

Only few studies involved repeat biopsies in a large number of obese subjects after a diet or a restrictive procedure. As early as 1970, Drenick et al[22] reported that extensive weight reduction by dieting or fasting in obese patients was accompanied by a marked decrease in the amount of fatty infiltration in the liver. Other authors have also noted regression of liver steatosis in obese persons after gastroplasty[23] or after diet and exercise.[24] However, these three studies had a small number of patients (17 or fewer) and only reduction of steatosis showed statistical significance.

Although two other studies showed similar significant improvement of liver steatosis in morbidly obese subjects with drastic weight loss induced by a very-low-calorie diet[25] and by gastroplasty,[26] in some patients liver histology (steatohepatitis) actually deteriorated.

Significant resolutions of steatosis, necroinflammatory change and fibrosis were demonstrated in another study,[27] after a mean excess weight loss of 52%. Although these observations are consistent with our findings, this was a series of 36 selected obese patients that were treated with laparoscopic adjustable gastric banding. Moreover, there were no extensive changes in the presence of lipogranulomas and no patient had a third serial liver biopsy.

Recently published data[28] demonstrate that steatosis and features of steatohepatitis can improve spontaneously over time, whereas fibrosis tended to progress with considerable variability. Although that was a large series of 103 patients, only 67% of the subjects were obese. Two other similar studies[29,30] have assessed the natural history of NASH, but not all patients were obese and the conclusions remain limited due to small numbers. A recent study showed a dramatic decrease in liver size, presumed to be loss of fatty infiltration, in only 2 weeks on a very-low-calorie diet.[31]

In this study, fasting glucose and biochemical variables reflecting lipid metabolism and liver func-

Table 5. Analysis of the association between clinical characteristics, changes in histological features and the changes in laboratory data. Intercorrelations between changes in histological features (1st vs 2nd biopsy)

	C Steatosis	C Steatohepatitis	C Fibrosis	C Lipogranulomas	C Regeneration
Age	NS	NS	NS	NS	NS
C BMI	NS	0.354*	NS	NS	NS
C Steatosis		0.665**	0.338*	0.302*	NS
C Steatohepatitis	0.665**		NS	0.386**	NS
C Fibrosis	0.338*	NS		NS	NS
C Lipogranulomas	0.302*	0.386**	NS		NS
C Regeneration	NS	NS	NS	NS	
C Fasting glucose	NS	NS	NS	NS	NS
C AST	0.388**	NS	NS	NS	NS
C ALT	0.332*	0.302*	NS	NS	NS
C Alkaline phosphatase	NS	NS	NS	NS	NS
C γ-GT	NS	NS	NS	NS	NS
C Bilirubin total	NS	NS	NS	NS	NS
C Total cholesterol	-0.376**	-0.352*	NS	NS	NS
C Triglycerides	NS	NS	NS	NS	NS
C HDL cholesterol	NS	NS	NS	NS	NS
C LDL cholesterol	-0.356*	-0.323*	NS	NS	NS
C Protein	NS	NS	NS	NS	NS
C Albumin	NS	NS	NS	NS	NS
C Globulins	NS	NS	NS	NS	NS
C Fibrinogen	-0.362**	NS	NS	NS	NS
C INR	NS	NS	NS	NS	NS

Spearman rank correlation coefficient, **C = Change**, BMI = Body Mass Index, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, γ-GT = gamma-glutamyl transpeptidase, HDL = High density lipoprotein, LDL = Low density lipoprotein, INR = International normalized ratio.
*Correlation is significant at 0.05 level (2-tailed). ** Correlation is significant at 0.01 level (2-tailed).

tion significantly improved after a massive weight reduction. Several reports have shown that weight reduction may be important for improving glucose metabolism[27,28,32-35] and reducing plasma lipids and lipoproteins.[27,33-36] Although some authors[17,25] observed no significant association between the degree of transaminase elevation and the histological features, we and others[18,21] showed that both serum transaminases were highly correlated with the degree of steatosis. We also found that the decrease of steatohepatitis was correlated positively with the decrease of ALT. Other authors[27,28] have reported that there is a significant positive correlation between the change in NASH and change in all enzymes related with liver function.

In summary, the major finding in the present study is that massive weight loss after VBG is significantly correlated with regression of NASH. Significant improvement of liver steatosis and significant overall decrease in severity of fibrosis and lipogranulomas were also noted. More importantly, we have confirmed all these alterations in a subgroup that continued to lose weight and had a third liver biopsy. Therefore, NASH is a potentially reversible condition in morbidly obese patients (86% regressed) after weight loss induced by VBG. On the other hand, liver fibrosis improved in nearly half (47%) of the patients.

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