

Improvement of Nonalcoholic Fatty Liver Disease After Bariatric Surgery in Morbidly Obese Chinese Patients

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Published online: 11 December 2011
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Abstract

Background Obesity is a risk factor for nonalcoholic fatty liver disease (NAFLD), which appears to improve after weight loss induced by bariatric surgery in Western countries. The present study aims to determine the alterations of clinical measurements and liver histology of NAFLD after bariatric surgery in morbidly obese Chinese patients.

Methods Between November 2006 and December 2007, 21 morbidly obese patients receiving intra-operative liver biopsy and follow-up liver biopsy 1 year after laparoscopic Roux-en-Y gastric bypass were enrolled. NAFLD activity score (NAS) and fibrosis stage were histologically evaluated.

Results The mean body mass index fell from 43.8 ± 7.5 to 28.3 ± 4.6 kg/m² ($P < 0.01$). Biochemical improvement was found in serum levels of alanine aminotransferase ($P < 0.01$) and γ -glutamyltransferase ($P < 0.01$), but not aspartate aminotransferase ($P = 0.66$). Histological improvement was noted in NAS ($P < 0.01$) and individual components, including

steatosis ($P < 0.01$), ballooning degeneration ($P < 0.01$), and lobular inflammation ($P = 0.02$). Pre-operatively, 4 (19.0%), 11 (52.4%), and 6 (28.6%) patients were found to have NAS ≥ 5 , 3 or 4, and ≤ 2 , respectively. All patients had NAS ≤ 2 after surgery. Fibrosis stage also showed significant improvement ($P < 0.01$).

Conclusions Bariatric surgery can achieve a dramatic improvement of NAFLD both biochemically and histologically in morbidly obese Chinese patients.

Keywords Nonalcoholic fatty liver disease · Nonalcoholic steatohepatitis · Obesity · Bariatric surgery · Liver biopsy

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
RYGB	Roux-en-Y gastric bypass
NAS	NAFLD activity score
BMI	Body mass index
LRYGB	Laparoscopic Roux-en-Y gastric bypass

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WC	Waist circumference
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	γ -Glutamyltransferase
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
HOMA	Homeostatic model assessment
SD	Standard deviation

Introduction

Nonalcoholic fatty liver disease (NAFLD) comprises a spectrum of disorders ranging from simple steatosis, nonalcoholic steatohepatitis (NASH) to fibrosis, which may even lead to cirrhosis, hepatocellular carcinoma, and end-stage liver disease [1, 2]. It is strongly associated with obesity and has become the most common liver disorder in Western countries [3]. The prevalence of NAFLD is about 70% in obese subjects and about 85–95% in morbidly obese subjects [4]. Among patients receiving bariatric surgery, hepatic steatosis can be found in most patients and NASH and cirrhosis can be found in about 25% and 1–3% of patients, respectively [5]. In addition to obesity, metabolic syndrome and insulin resistance are also associated with NAFLD. NAFLD is recognized as the hepatic representation of metabolic syndrome and insulin resistance is thought to play an important role in disease prevalence and progression of NAFLD [6–8].

Because of the lack of an effective pharmacologic therapy, treatment recommendations for NAFLD/NASH are based on lifestyle changes, including diet and exercise, to reduce weight. Weight loss can be beneficial in preventing and even reversing NAFLD; however, it is often difficult to achieve sustained weight loss in morbidly obese patients with diet and exercise alone. Bariatric surgery, especially Roux-en-Y gastric bypass, has proved to be effective for achieving sustained weight loss in these patients and is thought to be an attractive option in reversing many metabolic risk factors associated with NAFLD. Studies have shown that majority of patients achieve improvement or complete resolution of NAFLD, including steatosis, NASH, and fibrosis, after weight loss induced by bariatric surgery. Additionally, significant improvement has been seen in metabolic risk factors [4–6, 9–16].

With the increasing prevalence of obesity, the prevalence of NAFLD is also increasing in Eastern countries. NASH incidence was reported to be 35.5% in morbidly obese Chinese patients according to the definition of NAFLD activity score (NAS) [17]. Bariatric surgery is becoming more common in Asia and has been shown to have good efficacy in weight loss in morbidly obese Chinese patients

[18]. However, the efficacy of bariatric surgery for NAFLD in these patients remains unclear. This study aims to determine the alterations of clinical measurements and liver histology of NAFLD after bariatric surgery in morbidly obese Chinese patients.

Materials and Methods

Eligible Patients

Morbidly obese Chinese patients, defined as those with body mass index (BMI) ≥ 40 kg/m² or BMI ≥ 35 kg/m² with comorbidity, were evaluated by a multidisciplinary team consisting of dietitians, endocrinologists, gastroenterologists, psychiatrists, and surgeons in E-Da Hospital, Kaohsiung, Taiwan. Those who were unable to reduce weight by at least 6 months of diet, behavior modification, and pharmacologic therapy were considered for bariatric surgery.

Between November 2006 and December 2007, 21 morbidly obese patients who received a wedge liver biopsy taken from the edge of the right lobe of the liver at the beginning of the surgical procedure and a follow-up percutaneous needle biopsy with a 16-gauge biopsy needle (Medical Device Technologies Inc., Gainesville, FL, USA) 1 year after laparoscopic Roux-en-Y gastric bypass (LRYGB) were enrolled for analysis.

Exclusion criteria included the presence of daily alcohol intake of more than 20 g per day; chronic hepatitis B or C virus infection; use of hepatotoxic drugs; other known liver diseases such as Wilson's disease, hemochromatosis, α 1-antitrypsin deficiency, or autoimmune hepatitis; and malignant diseases. Written informed consent was obtained from each participant, and the ethical committee of E-Da hospital approved the study.

Anthropometric and Biochemical Measurements

Anthropometric and biochemical measurements were obtained at the time of first and follow-up liver biopsies for all subjects. Anthropometric measurements obtained included body weight, body height, waist circumference (WC), and hip circumference. Biochemical measurements included aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltransferase (GGT), serum cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol, uric acid, blood glucose level, and fasting insulin level. Serum leptin concentration was measured using a commercially available radioimmunoassay kit (LINCO Research, St. Charles MO, USA). Patients with elevated liver enzymes were defined as having a serum AST and/or ALT higher than the upper limit of normal (40 IU/L).

Definitions of Metabolic Syndrome and Insulin Resistance

We compared changes in metabolic syndrome and insulin resistance at two time periods between the first and follow-up liver biopsies. The presence of metabolic syndrome is defined by abnormal values for three or more of the following measurements: WC ≥ 90 cm for men or ≥ 80 cm for women, serum triglyceride levels ≥ 150 mg/dL, high-density lipoprotein cholesterol levels < 40 mg/dL in males and < 50 mg/dL in females, blood pressure $\geq 130/85$ mm Hg, and serum glucose levels ≥ 100 mg/dL. Those receiving anti-diabetic or antihypertensive therapy were assumed to have high fasting glucose levels or high blood pressure, respectively [19].

Insulin resistance was determined by the homeostatic model assessment method (HOMA), in which higher values of HOMA represent greater degrees of insulin resistance [20]. The HOMA for insulin resistance was deduced in this model according to measurements of fasting glucose and insulin. Briefly, the equation is: $\text{HOMA} = (\text{insulin} \times \text{glucose})/22.5$, where insulin is expressed in $\mu\text{U/mL}$ and glucose in mmol/L [20].

Histological Examination

Biopsy specimens were routinely stained with hematoxylin and eosin and Masson's trichrome. Two independent pathologists (Hwang JC and Chiang H) who were unaware of the patients' clinical and biochemical data evaluated the biopsy specimens. After an initial independent review of the slides, those with discrepancy were read by both pathologists to reach a consensus diagnosis. To avoid the interference of subcapsular fibrosis, we only estimated perisinusoidal and portal/periportal fibrosis on wedge biopsy specimens.

Histopathology was assessed according to the guidelines established by Kleiner et al. [21]. The NAS and fibrosis stage for each biopsy specimen was established. Steatosis is graded on 0 to 3 points: (0) steatosis $<5\%$, (1) steatosis 5–33%, (2) steatosis 33–66%, and (3) steatosis $>66\%$. Lobular inflammation is scored according to numbers of foci of inflammatory infiltration per $\times 200$ microscopic field, (0) no inflammation, (1) less than two foci, (2) two to four foci, and (3) more than four foci. Ballooning degeneration is scored on 0 to 2 points: (0) none, (1) few balloon cells, and (2) many balloon cells. NAS is defined as the sum of the scores, ranging from 0 to 8. NAS of ≥ 5 is diagnostic of NASH, NAS of 3 or 4 is indeterminate, and NAS of ≤ 2 is not diagnostic of NASH. Fibrosis was staged as follows: (0) no fibrosis; (1) perisinusoidal or periportal fibrosis with three different patterns: (1A) mild, zone 3, perisinusoidal, (1B) moderate, zone 3, perisinusoidal fibrosis, and (1C) portal/periportal fibrosis; (2) perisinusoidal and portal/periportal fibrosis; (3) bridging fibrosis; and (4) cirrhosis.

Statistical Analysis

For anthropometric and biochemical variables, data were presented as mean $\pm$ standard deviation (SD) for normally distributed continuous variables or as median (interquartile range) for continuous variables lacking a normal distribution, or as percentages for categorical variables. Changes between two biopsies were assessed using paired Student's *t*-test for parametric data, Wilcoxon signed rank test for nonparametric data, and McNemar test for categorical variables. Histological scoring was treated as ordinal categorical variables and changes in scoring between two biopsies were assessed using the nonparametric Wilcoxon signed rank test. A *P* value < 0.05 indicated a statistically significant difference. All analyses were performed by SPSS 12.0 version for WINDOWS.

Results

Effects of Bariatric Surgery on Anthropometric and Biochemical Measurements

There were 13 women and 8 men with a mean age of 29.9 ± 8.1 years. Four and three patients had history of hypertension and diabetes mellitus, respectively, but none of them received anti-diabetic or antihypertensive therapy. All patients had at least one of four abnormal findings on intra-operative biopsy specimens, including steatosis, lobular inflammation, ballooning degeneration, and fibrosis. During the follow-up period, the mean BMI fell from 43.8 ± 7.5 to 28.3 ± 4.6 kg/m^2 ($P < 0.01$) and the mean percentage of excess weight loss was $71.7\% \pm 12.7\%$.

Table 1 represents alterations of anthropometric and biochemical measurements between pre-bariatric surgery and 1-year post-bariatric surgery. Accompanying weight loss, waist circumference ($P < 0.01$), and waist-to-hip ratio ($P < 0.01$) also showed significant improvement. Parameters for metabolic syndrome ($P < 0.01$) and insulin resistance ($P < 0.01$) significantly improved after surgery. Twelve patients (57.1%) had metabolic syndrome before surgery, compared to only one patient (4.8%) who did after surgery. Additionally, all five components of metabolic syndrome showed significant improvement. Biochemical improvement was found in serum levels of ALT ($P < 0.01$) and GGT ($P < 0.01$), but not in AST ($P = 0.66$). With a threshold of 40 IU/L used as the upper normal range, preoperative AST and ALT levels were found to be abnormal in three (14.3%) and ten (47.6%) patients, respectively. Only one patient had a slightly abnormal level of AST (4.8%, $P = 0.5$) and no one had abnormal levels of ALT after surgery. Other biochemical variables including fasting glucose, triglyceride, cholesterol, LDL-cholesterol, and leptin levels were significantly

Table 1 Effects of LRYGB on clinical and biochemical measurements

Characteristics	Before surgery (<i>n</i> =21)	After surgery (<i>n</i> =21)	<i>P</i> value
Age (years)	29.9 (8.1)	30.9 (8.1)	–
Male gender, <i>n</i> (%)	8 (38.1)	8 (38.1)	–
BMI (kg/m ²), mean (SD)	43.8 (7.5)	28.3 (4.6)	<0.01
Waist circumference (cm), mean (SD)	120.4 (17.9)	90.0 (11.4)	<0.01
Waist-to-hip ratio, mean (SD)	0.91 (0.07)	0.86 (0.08)	<0.01
SBP (mmHg), mean (SD)	133.2 (12.1)	120.3 (10.1)	<0.01
DBP (mmHg), mean (SD)	82.8 (10.6)	73.3 (9.1)	<0.01
Glucose (mg/dl), median (IQR)	97.0 (17.0)	88.0 (9.0)	<0.01
Insulin (μU/ml), median (IQR)	20.4 (15.1)	3.9 (4.2)	<0.01
HOMA, median (IQR)	4.7 (6.0)	0.9 (0.9)	<0.01
AST level (IU/L), median (IQR)	27.0 (14.5)	27.0 (8.0)	0.66
ALT level (IU/L), median (IQR)	34.0 (31.0)	24.0 (13.5)	<0.01
GGT level (IU/L), median (IQR)	28.0 (30.0)	12.0 (7.0)	<0.01
Triglyceride (mg/dl), median (IQR)	126.0 (89.0)	68.0 (32.5)	<0.01
Cholesterol (mg/dl), median (IQR)	191.0 (35.0)	154.0 (44.5)	<0.01
HDL-cholesterol (mg/dl), median (IQR)	44.0 (14.5)	57.0 (12.5)	<0.01
LDL-cholesterol (mg/dl), median (IQR)	128.0 (40.0)	79.0 (43.0)	<0.01
Uric acid (mg/dl), median (IQR)	7.1 (2.3)	5.6 (3.0)	<0.01
Leptin (μg/L), median (IQR)	29.0 (17.0)	4.1 (10.5)	<0.01
Metabolic syndrome, <i>n</i> (%)	12 (57.1)	1 (4.8)	<0.01
Waist circumference ≥ 90 cm for men or ≥ 80 cm for women	21 (100.0)	12 (57.1)	<0.01
Hypertension or BP ≥ 130/85 mmHg	11 (52.4)	4 (19.07)	0.04
Diabetes or fasting glucose ≥ 110 mg/dL	6 (28.6)	0 (0)	0.02
Triglyceride ≥ 150 mg/dL	9 (42.9)	0 (0)	0.01
HDL- cholesterol < 40 mg/dL in men or < 50 mg/dL in women	13 (61.9)	3 (14.3)	<0.01

LRYGB laparoscopic Roux-en-Y gastric bypass, *BMI* body mass index, *SD* standard deviation, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IQR* interquartile range, *HOMA* homeostatic model assessment method, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* γ-glutamyltransferase, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *BP* blood pressure

reduced, and the HDL-cholesterol level was significantly increased.

Effects of Bariatric Surgery on Histological Parameters

Wedge biopsy specimens were about 2×2 cm in size, and needle biopsy specimens had a mean length of 16.4±2.6 mm and an appropriate number of portal tracts to enable a confident evaluation of histologic features and diagnosis. As shown in Table 2, significant improvement was seen in all histological parameters. According to NAS, four patients (19.0%) were diagnosed as NASH and 11 patients (52.4%) were diagnosed as indeterminate for NASH before surgery, but all patients had NAS of ≤2 after surgery (Fig. 1a). Before operation, 19 patients (90.5%) had steatosis; however, only one patient still had steatosis with a score of 1 after surgery. Among the 18 patients (85.7%) with ballooning degeneration before surgery, 11 patients improved after surgery and the remaining seven patients with a score of 1 remained unchanged after surgery. Lobular inflammation

was found in 15 patients (71.4%) and six patients (28.6%) before and after surgery, respectively. Among the six patients with lobular inflammation after surgery, five patients had an increased score, including three patients from 0 to 1 and two patients from 1 to 2. One patient with a score of 1 remained unchanged after surgery. Eighteen patients (85.7%) had fibrosis before surgery. Among them, 12 and six patients had stages 1 and 2, respectively. Fibrosis scores improved in 11 patients and remained unchanged in seven patients. All patients had fibrosis stage ≤2 before surgery and ≤1 after surgery (Fig. 1b).

Safety Profile

Three of the 21 patients had postoperative complications, but none had a major complication which was defined as a life-threatening event or a need for a repeat operation. Two patients had stenosis of gastrojejunostomy and one patient had bleeding from ulcer at gastrojejunostomy. However, they were successfully treated with medications or endoscopy.

Table 2 Effects of LRYGB on histological parameters

Characteristics	Before surgery (n=21)	After surgery (n=21)	P value
NAS, n (%)			
0	0 (0)	8 (38.1)	<0.01
1	3 (14.3)	8 (38.1)	
2	3 (14.3)	5 (23.8)	
3	3 (14.3)	0 (0)	
4	8 (38.1)	0 (0)	
5	4 (19.0)	0 (0)	
Steatosis, n (%)			
0	2 (9.5)	20 (95.2)	<0.01
1	8 (38.1)	1 (4.8)	
2	8 (38.1)	0 (0)	
3	3 (14.3)	0 (0)	
Ballooning degeneration, n (%)			
0	3 (14.3)	12 (57.1)	<0.01
1	16 (76.2)	9 (42.9)	
2	2 (9.5)	0 (0)	
3	0 (0)	0 (0)	
Lobular inflammation, n (%)			
0	6 (28.6)	15 (71.4)	0.02
1	13 (61.9)	6 (28.6)	
2	2 (9.5)	0 (0)	
Fibrosis, n (%)			
0	3 (14.3)	9 (42.9)	<0.01
1 (Ia/Ib/Ic)	12 (7/5/0) (57.1)	12 (6/6/0) (57.1)	
2	6 (28.6)	0 (0)	
3	0 (0)	0 (0)	
4	0 (0)	0 (0)	

LRYGB laparoscopic Roux-en-Y gastric bypass, NAS nonalcoholic fatty liver disease activity score

Discussion

To our knowledge, the present study reported first data on significant improvement of biochemical and histological measurements of NAFLD 1 year after bariatric surgery in morbidly obese Chinese patients. Metabolic factors, including

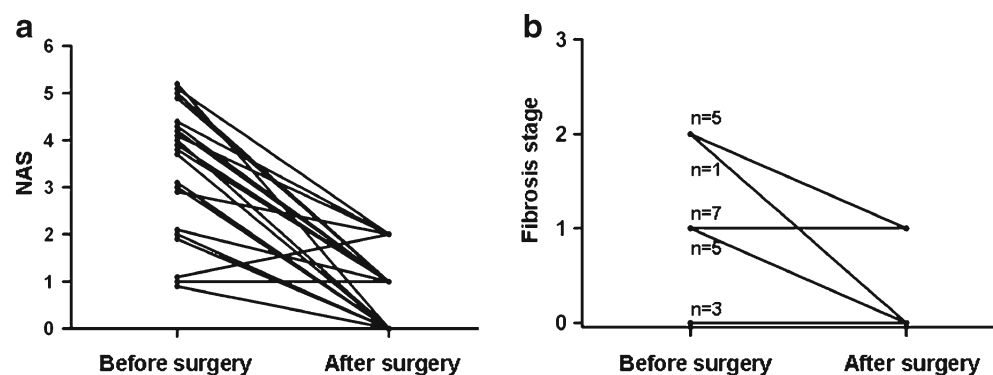
metabolic syndrome and insulin resistance, also improved significantly. A significant improvement was noted in all histological features of NAFLD, including steatosis, steatohepatitis, and fibrosis, at 1 year after bariatric surgery. No significant complication developed after and during the 1-year follow-up period.

In spite of different histopathologic grading systems used in Western countries, good effect of bariatric surgery on NAFLD was shown in a meta-analysis which enrolled 15 studies and a total of 766 subjects [22]. The percentage of patients with improvement in steatosis, steatohepatitis, and fibrosis was 91.6%, 81.3%, and 65.5%, respectively. Consistent with the reported data from Western countries, we also observed a striking improvement of steatosis; 18 of the 19 patients (94.7%) with steatosis had complete resolution. Another impressive finding is the resolution of NAS from diagnostic or indeterminate NASH (NAS ≥ 3) to absence of NASH (NAS ≤ 2) 1 year after surgery in all of our patients with NAS ≥ 3 . This result is substantially better than those published in Western countries (69.5%) [22]. The relatively lower severity of NAS in our series with a highest NAS of 5 might contribute to our better results. Whether there exists ethnic difference in the effects of bariatric surgery on improving NASH between Asian and Western population remains subject for further studies.

In the present study, we only estimated perisinusoidal and portal/periportal fibrosis and excluded subcapsular fibrosis to reduce the potential interference [23]. Improvement in fibrosis was observed in 11 of 18 patients (61.1%) with fibrosis 1 year after surgery in the current study, which is similar to previously reported results [22]. Nevertheless, a recent study on the long-term effect of bariatric surgery on NAFLD observed a slight increase of fibrosis 5 years after bariatric surgery for severe obesity in Western countries [24]. The long-term effects of bariatric surgery on NAFLD in Chinese morbidly obese patients remain to be studied.

In the present study, significant improvements were found in serum levels of ALT and GGT, but not in AST values ($P=0.66$). Studies have shown that a significant improvement of liver function tests can be achieved after

Fig. 1 Individual change of nonalcoholic fatty liver disease activity score (a) and fibrosis stage (b) after surgery



bariatric surgery-induced weight loss [9, 16]. However, no significant changes in AST have also been reported [13]. One possible explanation is that only three patients (14.3%) had abnormal AST values prior to surgery in this study. Although all of them but one had normal AST results after surgery, the change still did not reach statistical significance.

There are limitations in the current study. First, the sample size is relatively small and only 21 patients were enrolled. Secondly, because of the absence of a control group, the efficacy of bariatric surgery cannot be compared with other weight reduction programs such as diet or exercise in this study. However, no randomized trial studying the effect of bariatric surgery on NAFLD has been reported so far [25].

In summary, we demonstrated that bariatric surgery can safely achieve a dramatic improvement of NAFLD, both biochemically and histologically, in morbidly obese Chinese patients.

Acknowledgements This study was supported by a project of the E-Da Hospital, grant number EDAHP-98-015.

Disclosure The authors declare no conflict of interest.

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