

# Prevalence and Predictors of Asymptomatic Liver Disease in Patients Undergoing Gastric Bypass Surgery

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**Background:** Nonalcoholic steatohepatitis (NASH) is a form of fatty liver disease that is increasingly recognized. There are limited data on the prevalence of NASH and the role of risk factors for NASH among the morbidly obese.

**Hypothesis:** The prevalence of asymptomatic NASH among morbidly obese patients undergoing gastric bypass surgery is high, and there are identifiable risk factors for NASH.

**Design:** Prospective case study.

**Setting:** University hospital.

**Patients:** Forty-eight consecutive patients undergoing gastric bypass surgery who had a concurrent open liver biopsy. Exclusion criteria included current consumption of more than 2 alcohol beverages monthly and known cirrhosis. A hepatopathologist blinded to clinical data reviewed biopsy specimens.

**Main Outcome Measures:** The presence of NASH or severe fibrosis, preoperative body mass index (BMI) (calculated as weight in kilograms divided by the square of

height in meters), fasting triglyceride level, and presence of type 2 diabetes mellitus (DM).

**Results:** Patients (mean  $\pm$  SD age, 42  $\pm$  10 years; 33 women) had an initial mean BMI of 59.9  $\pm$  12. Thirty-one patients (65%) had moderate to severe steatosis. Only 6 (12%) had advanced fibrosis. Sixteen (33%) had evidence of NASH. There was no difference in mean age, sex, BMI, or fasting triglyceride level between patients with and without NASH or advanced fibrosis. The odds of NASH were 128 times greater (95% confidence interval [CI], 5.2-3137.0) and the odds of severe fibrosis 75 times greater (95% CI, 4.5-1247.0) in patients with DM than in those without DM. Preoperative BMI was not independently associated with NASH (odds ratio, 1.01; 95% CI, 0.9-1.1) or severe fibrosis (odds ratio, 0.9; 95% CI, 0.86-1.02) after adjustment for DM.

**Conclusions:** Moderate to severe hepatic steatosis and NASH are common among individuals undergoing gastric bypass procedures. Diabetes mellitus but not BMI is associated with NASH and advanced hepatic fibrosis in these patients.

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**T**HE EPIDEMIC of obesity in the United States has been linked to an unprecedented increase in diseases of the heart, lungs, kidney, and liver. Nonalcoholic fatty liver disease (NAFLD) in the adult population in the United States is now common, with prevalence estimated at 23%.<sup>1</sup> Nonalcoholic fatty liver disease is found in 65% of obese patients and is speculated to involve close to 90% of those who are morbidly obese. While NAFLD is considered relatively benign, nonalcoholic steatohepatitis (NASH), with progression to fibrosis, is an increasingly identified aggressive variant that has a considerable impact on patient health. Nonalcoholic steatohepatitis and fibrosis may progress to cirrhosis and end-stage

liver disease. In an autopsy series of unselected patients, 6.2% exhibited histologic traits consistent with NASH,<sup>2</sup> and the rate seems to be rising. In many of the cases of NASH, the disease remains asymptomatic until advanced liver disease has developed. Because of the casual link between obesity and NASH and its early, asymptomatic course, this might represent a true public health threat for the next generation. Given the connection between NAFLD and obesity, there is surprisingly little information available regarding the prevalence of asymptomatic liver disease among morbidly obese patients. This population is increasingly undergoing gastric bypass procedures in an effort to improve quality of life and to address comorbid conditions. A more com-

plete assessment of these comorbid conditions is important in evaluating outcomes of gastric bypass procedures.

Predicting and preventing the development of advanced liver disease in patients with obesity has been challenging. Multiple triggers may be necessary to develop progressive NASH. Such factors may include type 2 diabetes mellitus (DM), increasing levels of body mass index (BMI), hepatotoxins, ethanol, tumor necrosis factor  $\alpha$ , endotoxemia, viral infection, fatty acid up-regulation, mitochondrial maladaptation, and iron overload. To date, however, the relative importance of these risk factors has yet to be completely determined. Determining the prevalence of liver disease and the role of certain predictors of advanced disease in the obese patient is important as we begin to try and assess the global impact of gastric bypass surgery. The purpose of this study was to prospectively evaluate the prevalence of and risk factors for liver disease and NASH among morbidly obese patients undergoing gastric bypass procedures.

## METHODS

### PATIENT SELECTION

The study group was composed of 48 consecutive patients with a BMI (calculated as weight in kilograms divided by the square of height in meters) greater than 35 undergoing gastric bypass surgery at a single academic medical center between October 1, 1996, and September 30, 1999. (The 85th percentile of BMI for US adults aged 20-29 years is 27.8. A BMI greater than 35 is morbidly obese and greater than 55 is considered super-obese.<sup>3</sup>) The patients underwent intraoperative hepatic fine-needle biopsy at the time of gastric bypass surgery.

Exclusion criteria included age younger than 18 years, current (past 12 months) consumption of more than 2 alcoholic beverages monthly, known cirrhosis or other liver disease, and previous jejunoileal bypass surgery. Medications were reviewed to exclude drugs known to produce hepatic steatosis, including methotrexate, tetracycline, calcium channel blockers, amiodarone, high-dose estrogens, or corticosteroids taken in the past 6 months.<sup>4</sup> Fasting triglyceride level, an assessment of past and present ethanol intake, BMI, age, sex, and the presence of DM were recorded. The diagnosis of DM was defined as present if any of the following were identified: self-reported clinician diagnosis of DM, random serum glucose level greater than 170 mg/dL (9.4 mmol/L), oral glucose tolerance test findings with 2-hour plasma glucose level greater than 199 mg/dL (11.0 mmol/L), or fasting plasma glucose levels greater than 125 mg/dL (6.9 mmol/L). It is inherently difficult to ascertain the nondrinking status of patients with NASH due to the lack of a sensitive and specific marker of alcoholism. Heavy ethanol use was defined as history of alcohol dependence by standard clinical criteria, excessive ethanol consumption (ie,  $\geq 20$ g/d in women and  $\geq 30$  g/d in men), or known alcoholic liver disease. Available laboratory data were reviewed for serologic and liver function test results to exclude other potential causes of liver disease.

This study was approved by the University of Washington Institutional Review Board.

### LIVER HISTOLOGIC CHARACTERISTICS

An intraoperative liver fine-needle biopsy specimen was obtained from all patients and stained with hematoxylin-eosin, Masson trichrome, and periodic acid-Schiff (PAS) with dia-

stase stains. All specimens were considered sufficient for analysis. Pathologists (P.E.) without knowledge of the patient's background clinical and biochemical data read all liver biopsy results. The biopsy results were then reviewed by a hepatopathologist and hepatologist blinded to clinical data. The degree of fibrosis was assessed using a 5 grade (Ishak) scale, with 0 indicating none, normal connective tissue; 1, mild, foci pericellular fibrosis in zone 3; 2, moderate, perivenular, or perisinusoidal fibrosis confined to zone 3 and two regions with or without portal and/or periportal fibrosis; 3, severe, bridging or septal fibrosis; and 4, cirrhosis. Advanced fibrosis was defined as level 3 or 4 fibrosis. The level of fatty infiltration was assessed on a scale of 1 to 3, with 1 indicating mild (10% to 30% of hepatocytes affected); 2, moderate (30% to 70% of hepatocytes affected); and 3, severe (more than 70% of hepatocytes affected).<sup>5</sup> The degree of inflammation was also graded on a scale of 1 to 3 (1, mild; 2, moderate; 3, severe). Presence of Mallory bodies and ballooning degeneration was recorded. The histological definition of NASH was based on steatosis plus two of these three zone 3 (centrilobular) criteria: (1) necroinflammatory intra-lobular foci with mononuclear cells and/or neutrophils; (2) ballooning degeneration of hepatocytes with or without Mallory bodies; and (3) perisinusoidal fibrosis among zone 3 hepatocytes.<sup>6,7</sup>

### STATISTICAL ANALYSIS

The  $\chi^2$  and Fisher exact tests were used to compare categorical variables. The *t* test (2-tailed) was used to compare continuous variables. The association of NASH and/or fibrosis with age, sex, BMI, diabetes, alcohol use, and hypertriglyceridemia was evaluated using a logistic regression model. An  $\alpha$  value of .05 was selected as the threshold value below which statistical significance was declared.<sup>8</sup> Data were analyzed using Stata version 7.0 statistical software (Stata Corp, College Station, Tex).

## RESULTS

### PATIENT DEMOGRAPHICS AND LABORATORY EVALUATION

Patients (mean  $\pm$  SD age, 42  $\pm$  10 years; 33 women) had an initial mean  $\pm$  SD BMI of 59.9  $\pm$  12 (median BMI, 57). Nine (19%) had DM, and 11 (23%) had baseline hypertriglyceridemia (mean fasting triglyceride level of 185 mg/dL [2.09 mmol/L]). Twenty-eight patients (58%) had a BMI greater than 55, considered to be morbidly super-obese. No patients had ascites detected clinically. Nine (19%) of the patients currently drank 1 or 2 alcoholic beverages per month, and 5 (10%) had a distant history of heavy ethanol use. All of these patients had been abstinent a minimum of 4 years. The duration of prior heavy ethanol use in these 5 patients ranged from 2 to 8 years, with a median of 4 years.

### LIVER HISTOLOGIC CHARACTERISTICS

Liver biopsy results are summarized in **Table 1**. Forty-one (85%) of 48 patients had hepatic steatosis. Thirty-one patients (65%) had moderate to severe steatosis. Twenty-four (50%) of 48 had lobular inflammation; 17 (35%) of 48 had fibrosis. Six (12%) had bridging fibrosis. Sixteen (33%) met all histologic criteria for NASH. None had well-established cirrhosis.

**Table 1. Hepatic Histologic Characteristics in 48 Patients**

Characteristic	Patients, No. (%)
Degree of fibrosis	
2	17 (35)
3	6 (12)
4	0
Degree of steatosis	
0	7 (15)
1	10 (21)
2	16 (33)
3	15 (31)
Mallory bodies	7 (15)
Lobular inflammation	24 (50)
Ballooning degeneration	15 (31)
NASH	16 (33)

Abbreviation: NASH, nonalcoholic steatohepatitis.

### FACTORS ASSOCIATED WITH THE PRESENCE OF NASH OR FIBROSIS

Using univariate analysis, DM was significantly associated with the presence of NASH ( $P < .001$ ), whereas age, BMI, sex, and history of ethanol intake were not significant (**Table 2**). Using logistic regression, only DM was independently associated with NASH, with the odds of NASH in patients with DM being 128 times greater (95% confidence interval [CI], 5.2-3137.0) than in patients without DM (**Table 3**). Preoperative BMI was not independently associated with NASH (odds ratio, 1.01; 95% CI, 0.9-1.1). The degree of steatosis and NASH were highly correlated. The odds of NASH increased 2.2 (95% CI, 1.2-3.8) for each unit of increase in the degree of steatosis.

### FACTORS ASSOCIATED WITH ADVANCED FIBROSIS

Of the 9 diabetic patients, 7 (77%) had advanced fibrosis, but there was no relationship between BMI, age, sex, fasting triglyceride level, or alcohol use between patients with and without advanced fibrosis (Table 2). Eighteen patients had hepatic fibrosis of Ishak levels 2 to 4, including all 5 patients with a history of distant ethanol abuse, but 12 patients with fibrosis levels 2 to 4 had no current ethanol ingestion and an unremarkable ethanol history. When controlling for BMI, the odds of severe fibrosis were 75 times greater (95% CI, 4.5-1247.0) in diabetic patients than in those without DM. Preoperative BMI was not independently associated with severe fibrosis (odds ratio, 0.9; 95% CI, 0.86-1.02).

### COMMENT

Liver disease is the second leading cause of death in patients with NAFLD,<sup>7</sup> and among patients with NASH, cirrhosis- and liver-related deaths occur in 25% and 8% of patients over a 10-year period.<sup>9</sup> Our study demonstrates that among otherwise asymptomatic, morbidly obese individuals undergoing gastric bypass surgery, moderate to severe hepatic steatosis is quite common, with NASH identified in 33% of cases. Understanding the predic-

tors of advanced disease is more problematic. Hepatic steatosis results from an inappropriately high level of free fatty acids delivered to the liver. It is increasingly accepted that a second trigger is necessary for steatosis to progress to the necroinflammatory state of NASH.<sup>10</sup> Examples of other triggers have been suggested, including DM, higher BMI levels, hepatotoxins, ethanol use, tumor necrosis factor  $\alpha$ , endotoxemia, viral infection, fatty acid up-regulation, mitochondrial maladaptation, and iron overload. Our study demonstrated that DM, but not BMI, is associated with NASH and advanced hepatic fibrosis. These findings suggest that obesity alone is not sufficient to induce NASH or its more aggressive variant.

To date there have been limited data available on the prevalence of asymptomatic NASH among morbidly obese individuals and the risk factors for progression to fibrosis. The presence of advanced hepatic fibrosis in liver biopsy findings of all patients with NASH is estimated at 15% to 50%, and cirrhosis is noted in 7% to 26% of patients at the time of diagnosis.<sup>2,11,12</sup> We found a lower rate of fibrosis in this asymptomatic population (12%) than is commonly identified and no evidence of cirrhosis. In light of the prospective design of this study, one explanation may include referral bias in other published reports, but the exclusion criteria that applied to pre-existing liver disease may also be related.

In determining the risk factors for NASH, investigators<sup>2</sup> have used postmortem data and found that DM, severity of obesity, weight loss within past 30 days of life, and female sex were all related to NASH. In that retrospective analysis among morbidly obese patients with NASH, 13.8% had advanced fibrosis. Fibrosis in this report was associated with DM, obesity, and severity of steatosis. Other investigators have evaluated risk factors for fibrosis in NASH prospectively.<sup>13,14</sup> In these studies, patients older than 45 years and those who were obese and/or diabetic were the individuals at greatest risk of advanced hepatic fibrosis. In the age group older than 45 years, 40% had advanced fibrosis,<sup>13</sup> and age and DM seemed to be effect modifiers in the association with fibrosis. When DM and obesity were present in the older group, the percentage with advanced fibrosis rose to 60%. In the group younger than 45 years, only 4% had advanced fibrosis, and if DM and obesity were present, the rate rose to 8%. A similar, prospective evaluation by Dixon et al<sup>15</sup> evaluated 105 severely obese individuals (40 of whom were actively drinking 20-200 g/wk of pure ethanol) who underwent intraoperative liver biopsies. They found that 26% had NASH, and 11 (42% of those with NASH) had advanced fibrosis. In that study systemic hypertension, elevated insulin resistance index (a combined effect of fasting glucose and fasting insulin levels), and serum alanine aminotransferase levels were significant independent predictors of NASH. It is important to note that this group included patients with isolated portal fibrosis and those who were currently drinking excessive amounts of ethanol, whereas our study controlled for current and remote alcohol use.

The pathophysiologic linking of NAFLD, NASH, and fibrosis is complex and an area of intense scrutiny that is important in trying to understand the role of gastric bypass procedures in the natural history of NASH. One

**Table 2. Univariate Analysis of Patient Variables Between Those With and Without Fibrosis or NASH**

Variable	Presence of NASH		Presence of Fibrosis	
	No NASH	NASH	No Fibrosis	Fibrosis
Age, mean, y	42.5	40.1	41.4	43.5
Male, No./total No. (%)	9/32 (28)	6/16 (38)	11/42 (26)	4/6 (67)
BMI, mean $\pm$ SD, kg/m <sup>2</sup>	59.7 $\pm$ 12.6	60.2 $\pm$ 11.7	60.9 $\pm$ 12.3	53.0 $\pm$ 10.1
Fasting triglyceride level, mean $\pm$ SD, mg/dL (mmol/L)	158.9 $\pm$ 66.5 (1.8 $\pm$ 0.8)	243.5 $\pm$ 158.2 (2.8 $\pm$ 1.8)	166.7 $\pm$ 80.9 (1.9 $\pm$ 0.9)	344 $\pm$ 195 (3.9 $\pm$ 2.2)
Type 2 diabetes mellitus, No./total No. (%)	1/32 (3)	8/16 (50)*	4/42 (10)	5/6 (83)†
Distant heavy ethanol intake, No./total No. (%)	23/32 (72)	11/16 (69)	3/39 (7)	2/6 (33)

Abbreviations: BMI, body mass index; NASH, nonalcoholic steatohepatitis.

\* $P < .01$  compared with patients without NASH.

† $P < .01$  compared with patients without fibrosis.

possible cause of hepatocyte injury relates to insulin resistance. Sanyal et al<sup>16</sup> found insulin resistance was uniformly present in patients with NAFLD or NASH. Insulin resistance favors intramitochondrial fatty acid beta oxidation, and this results in increased intracellular levels of toxic free radicals.<sup>16-18</sup> In the presence of insulin resistance, there may be an increased risk of necroinflammation with progression to advanced fibrosis.<sup>15,16,19</sup> Although the etiologic factors associated with progression to the necroinflammatory state are not well delineated, cytokine sensitivity is increased in hepatic steatosis,<sup>19,20</sup> including increased CYP2E1 expression in NASH. Another consideration is that free fatty acids induce triglyceride synthesis, peroxisomal oxidation resulting in free radical formation, and fatty acid beta oxidation in mitochondria. Other mechanisms of injury may relate to the increase in reactive oxygen species production in fatty liver mitochondria<sup>19</sup> and that expression of hepatocyte alcohol-inducible cytochrome P4502E1 (CYP2E1) is increased in NASH.<sup>21</sup> Subsequent oxidative stresses in patients with NASH have been implicated in hepatocyte injury. The ability to reverse the effects of NASH in morbidly obese patients is a target area for further investigation.

The progression of NAFLD to NASH and fibrosis remains a major health concern. Our study helps to better understand the prevalence of asymptomatic liver disease in patients undergoing gastric bypass procedures and to quantify the effect of certain risk factors in the progression of disease. In patients who are noted to have asymptomatic NASH or steatosis during a gastric bypass operation, postoperative management is problematic. While weight loss is important in the management of NASH, gradual weight loss is preferred to the sudden weight loss that occurs after gastric bypass procedures. In fact, extreme weight loss over short periods of time may be associated with progression to advanced disease,<sup>22,23</sup> and the impact of surgical weight loss on NASH has not been evaluated. Given the findings of our study—that nearly 1 in 3 patients undergoing gastric bypass surgery has NASH—the potential impact of rapid weight loss on liver disease should be considered in preoperative assessments. For patients diagnosed with NASH, therapeutic interventions include dietary modifications, avoidance of hepatotoxic agents, and exercise and behavior

**Table 3. Logistic Regression of NASH Outcomes**

Variable	Odds Ratio (95% Confidence Interval)
Diabetes	128.1 (5.2-3137.0)
BMI	1.01 (0.9-1.1)
Sex	1.21 (0.2-7.4)
Age	0.92 (0.8-1.0)
Hypertriglyceridemia	0.54 (0.1-3.8)

Abbreviations: BMI, body mass index; NASH, nonalcoholic steatohepatitis.

modification.<sup>24</sup> Investigational pharmacologic agents for the treatment of NASH are in development and are not clinically available. Our research supports the practice of routine liver biopsy in patients undergoing gastric bypass procedures and continued investigation into the relationship of morbid obesity and rapid weight loss on the progression of NASH.

Limitations of this study may be linked to the unique features of our study population. Our patients were seen for morbid obesity, not for evaluation of abnormal liver enzymes and, in fact, were excluded from analysis if they had occult or known liver disease. Furthermore, our patients included a higher percentage of those with so-called superobesity than is typically considered in most surgical or medical evaluations of this issue. Any independent association of BMI and the development of NASH that might occur at lower BMIs may therefore have been missed by this study. Descriptions of diabetes rather than insulin resistance were used to describe patients; therefore, it is possible that some patients had undiagnosed diabetes. Conclusions based on this unique group therefore might not be generalizable to the population at large. Last, given the relatively small number of patients examined in this study, in instances when no differences in rates of NASH were identified based on patient characteristics (such as BMI, sex, age) a type II error cannot be excluded. A larger prospective evaluation would be required to address this issue and the evolution of NASH after gastric bypass procedures.

Given the prevalence of obesity in the US population, a more complete appreciation of obesity-related liver disease is important from a public health perspective. By better understanding the distribution and risk factors of

liver disease in patients with severe obesity, we can begin to assess the impact of interventions such as morbid obesity surgery on this important comorbidity. Furthermore, a complete assessment of the prognostic factors associated with NASH and progression to fibrosis is helpful in caring for patients at risk for liver disease.

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### Quotation

"Surgery is what a surgeon practices. An operation is what a surgeon performs. In this context, there is no such word as surgeries. In Great Britain, surgeries are treatment rooms. Neither an operation nor a patient is a case, but that's another commentary."

Source: Allen CJ. Surgeries. *Arch Surg*. 1996;131:128.