Effect of Body Mass Index on Nonalcoholic Fatty Liver Disease in Patients Undergoing Minimally Invasive Bariatric Surgery

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The risk factors for nonalcoholic fatty liver disease in patients undergoing bariatric surgery are under study. We wanted to determine the correlation between nonalcoholic fatty liver disease and patient factors such as obesity and liver function tests. A retrospective analysis was performed on 177 nonalcoholic morbidly obese patients who underwent laparoscopic Roux-en-Y gastric bypass with liver biopsy, to identify risk factors for nonalcoholic fatty liver disease. The histologic grade of liver disease was compared with preoperative body mass index, age, and liver function tests. Simple steatosis and steatohepatitis were present in 90% and 42% of patients, respectively. Elevated transaminaselevels were an independent risk for liver disease. Body mass index and liver disease were not correlated with univariate analysis. Regression analysis performed on age, body mass index, and liver disease demonstrated that the risk for liver disease increased with body mass index in the younger (<35 years old) age group and decreased with body mass index in the older (>45 years old) age group. There was a high incidence of steatosis and steatohepatitis in these nonalcoholic bariatric patients, and elevated transaminase level was indicative of disease. Body mass index was a positive risk factor for liver disease in younger patients but a negative risk factor in the older patients. (J GASTROINTEST SURG 2004;8:849–855)

KEY WORDS: Nonalcoholic fatty liver disease, morbid obesity, laparoscopic bariatric surgery

Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of excessive fat (5%–10% of organ weight) in the liver of individuals who consume no more than two alcoholic beverages per day.[1] The spectrum of NAFLD extends from fatty replacement (simple steatosis) to nonalcoholic steatohepatitis (NASH).[2] In adults, the typical histopathologic manifestations of NASH include steatosis (especially in zone 3, near the hepatic venules), ballooned hepatocytes, lobular inflammation, and zone 3 perisinusoidal fibrosis.[1] An autopsy study found simple steatosis and NASH in 70% and 18.5% of obese patients, respectively; these figures were 35% and 2.7% in nonobese patients, respectively.[3] Up to 11% of nonalcoholic obese patients with abnormal liver function tests but no clinical liver disease have histopathologic evidence of cirrhosis[4]; on a similar note, 10%–30% of patients with NAFLD develop cirrhosis after 10 years,[5–7] although only a minority have liver failure. The 5-year survival of patients diagnosed with NASH is 67%; death often is from comorbid disease.[8]

The pathophysiology of NASH has been described to follow a "two-hits hypothesis."[9] The first hit, or insult, to liver homeostasis involves accumulation of

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triglycerides in the liver (i.e., steatosis) secondary to overeating. This situation raises the level of intracellular oxidant stress, which in turn makes the hepatocyte vulnerable to a second insult. The second insult may involve an acute oxidant stress load, an upregulation of tumor necrosis factor α, or another environmental and/or genetic factor that can induce necrotic cell death in susceptible hepatocytes; this in turn will produce inflammation.[10] Considering the etiologic factors involved, it is not surprising that NASH is associated with diagnoses such as obesity, insulin-resistant diabetes, hyperlipidemia, hypertension, and the metabolic syndrome.[11]

The impact of NASH on operative mortality and long-term outcome in bariatric surgery is unclear. In one retrospective study of 126 surgeons who performed 86,500 bariatric procedures (via the open approach) in individuals not suspected to have liver disease, a grossly cirrhotic liver was found in 0.14% of patients.[12] The operative mortality rate in these cirrhotic patients was approximately five times that of bariatric patients without cirrhosis.[12] Whether the effect of unexpected cirrhosis on minimally invasive bariatric operative mortality will be similar to the effect observed on open operative mortality remains to be seen. Currently, there are no clinical or biochemical tests that accurately detect NASH[1,13]; a definitive diagnosis relies on liver biopsy.

In 2002, approximately 75,000 bariatric procedures were performed in the United States; in comparison, the annual rate was 10,000–15,000 in the mid 1990s.[14] One of the main factors responsible for this increase is the widespread application of minimally invasive bariatric procedures.[14] Such a large increase in the number of bariatric procedures (which, by most indicators, will continue to increase) combined with the evolving knowledge about NASH[1,10] led us to characterize the incidence of NASH in our bariatric population and to determine whether there were preoperative risk factors for NASH. We confirmed previously reported risk factors but also found an unexpected protective effect of body mass index (BMI) on NASH in older patients.

PATIENTS AND METHODS

Permission to review medical records for this study was obtained from the institutional review board. Between November 2001 and April 2003, data were collected on 177 nonalcoholic morbidly obese patients who underwent minimally invasive (laparoscopic) gastric bypass with liver biopsy, supervised by one surgeon (C.T.F.). Routine preoperative evaluation included history and physical examination (with BMI calculation), cardiopulmonary testing, and serologies, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), alkaline phosphatase (AP), total protein (TP), albumin (Alb), hepatitis panel, and human immunodeficiency virus testing.

The primary indication for bariatric surgery was BMI of greater than 40 (weight [kg]/height [m^2]); if a patient had a BMI of 35–40 and significant comorbidity attributable to obesity, the patient also was considered for a bypass.[15] The criterion for a "nonalcoholic" was two or fewer drinks per day (one drink = 12 oz. beer, 5 oz. wine, or 1.5 oz. liquor). All patients underwent a laparoscopic Roux-en-Y gastric bypass with intraoperative liver biopsy. There were no intraoperative or postoperative complications related to the liver biopsy. The diagnosis of NASH was based on the presence of steatosis and portal inflammation (with or without fibrosis, cirrhosis, or Mallory bodies) with the exclusion of other liver diseases such as alcoholic hepatitis, viral hepatitis, drug-induced hepatitis, hemochromatosis, and Wilson's disease.[1] The grading scales for steatosis and steatohepatitis are shown in Table 1.

The Kruskal-Wallis test (KaleidaGraph; Synergy Software, Reading, PA) was used to evaluate univariate relationships. The level of significance was defined as $p < 0.05$. Cumulative logit regression analysis using the SAS System for Windows (Cary, NC), Version 8.2 was performed to detect multivariate relationships. A backwards elimination procedure was used to determine important factors associated with steatohepatitis and steatosis. Variables included in the modeling process were age, BMI, sex, AST, ALT, TB, AP, and Alb along with two-level interactions for BMI and sex and BMI and age. Variables were retained in the model if they maintained a significance level of 0.05.

Table 1. Grading scales for steatosis and steatohepatitis

Steatosis		Steatohepatitis	
Grade	**Description**	**Grade**	**Description**
0	None	0	None
1	Mild	1	Mild pericellular fibrosis confined to zone 3
2	Moderate	2	Moderate pericellular fibrosis confined to zone 3 with no or minimal fibrosis
3	Severe	3	Severe septal fibrosis
		4	Cirrhosis

RESULTS

A consecutive group of 186 nonalcoholic obese patients (mean age, 40 years; median age, 40.0 years; age range, 18–68 years; 155 women [83%]) who underwent laparoscopic gastric bypass with liver biopsy was reviewed. The mean BMI was 48.9 kg/m^2 (median, 46.9 kg/m^2; range, 35–86 kg/m^2). Of this group, nine liver biopsies either were not obtained or were not readable secondary to insufficient specimen quantity, which left 177 biopsy samples for analysis. Of note, the planned operation was not altered if any of the 186 patients secondary to an intraoperative finding. The distribution of the various grades of steatosis and steatohepatitis is shown in Table 2. Only 10% of patients did not have any steatosis, and none of these patients had steatohepatitis. On the other hand, 58% of the patients did not have any steatohepatitis; in this group, the number of patients with grade 0, 1, 2, and 3 steatosis was 18, 63, 19, and 2, respectively.

Determination of a univariate relationship between either liver disease and other factors (age, BMI, AST, ALT, TB, AP, or Alb) is shown in Table 3 (steatosis) and Table 4 (steatohepatitis). For example, the average age of patients with grade 0, 1, 2, or 3 steatosis is shown in the first line of Table 3, along with the results of the Kruskal-Wallis test (the nonparametric equivalent of analysis of variance testing). In summary, Table 3 indicates that there was no simple correlation of steatosis versus age, BMI, TB, AP, or Alb; however, nonparametric testing of either AST or ALT against steatosis revealed that elevation of one or both of these transaminases was correlated with the presence of steatosis. Similarly, elevation of AST and/or ALT was correlated with the presence of steatohepatitis (Table 4), whereas none of the other factors correlated. Because there only was one patient with grade 3 (severe) steatohepatitis, this individual was grouped with the grade 2 patients for the analysis. Plots of the raw data for some of the variables examined in Tables 3 and 4 are shown in Fig. 1; these scattergrams reveal that at least some of the data have a nonnormal distribution (especially in Fig. 1, *A* and *B*, which show the AST data).

Consideration of three-variable relationships revealed an interaction among BMI, age, and presence of liver disease. To illustrate this relationship, some of the raw data are replotted (Fig. 2). The patients were segregated into five age ranges, and each age range was further segregated according to grade of steatosis (Fig. 2, *A*). The mean BMI of these age–grade "isobars" then was calculated and plotted. The plot suggests that younger patients with a higher BMI had greater risk of steatosis and that older patients with a higher BMI had less risk of steatosis (Fig. 2, *A*). Analogous findings are shown in Fig. 2, *B*; that is, the risk of steatohepatitis appears to be elevated in younger patients with a higher BMI, but the risk of steatohepatitis decreases with increasing BMI in the older age groups.

The putative relationship among BMI, age, and grade of disease was confirmed with cumulative regression analysis. For both steatosis and steatohepatitis, the interaction between age and BMI was significant ($P = 0.0106$ and 0.0010, respectively). At lower ages, as BMI increased, the probability of no disease increased. For the middle ages, there was little effect of BMI on the probability of no disease. At the higher ages, as BMI increased, the probability of no disease increased. In other words, the effect of BMI on the probability of disease in younger subjects was opposite the probability of disease in older subjects. For both steatosis and steatohepatitis, the regression analysis implied a BMI or an age at which the risk of disease is constant regardless of the other value; these BMI or age values (along with their confidence intervals) are given in Table 5. For example, there was no effect of BMI on the risk for steatohepatitis in a 40-year-old patient. Another interpretation of the model is that the odds of steatohepatitis were significantly increased with a 1-unit increase in BMI for ages 32 and younger and that the odds were significantly decreased with a 1-unit increase in BMI for ages 50 and older.

Table 2. Distribution of the various grades of steatosis and steatohepatitis

	No. of patients			
Liver disease	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**
Steatosis	18	71	65	23
Steatohepatitis	102	59	15	1

DISCUSSION

The clinical importance of cryptogenic hepatitis, of which NASH is commonly the underlying cause, is controversial.[13] The controversy appears to be related to the rate at which NAFLD progresses to clinical disease with complications of portal hypertension, hepatic insufficiency, and so on. For example, unsuspected cirrhosis was found in about 1:1000 bariatric patients in a worldwide questionnaire survey[12]; this statistic seems counter to the estimate that

Table 3. Correlation of various factors with the grade of steatosis

Factor	Grade of steatosis 0	1	2	3	*P* value
Age (yr)	34.7 ± 12.3 (18)	40.8 ± 11.0 (71)	42.2 ± 10.9 (65)	38.5 ± 11.1 (23)	0.0661
BMI (kg/m^2)	48.6 ± 10.3 (18)	48.7 ± 7.9 (70)	49.1 ± 9.0 (65)	50.4 ± 7.9 (23)	0.6049
AST (U/L)	19 ± 6 (18)	21 ± 8 (66)	31 ± 33 (63)	43 ± 46 (21)	<0.001
ALT (U/L)	22 ± 10 (18)	25 ± 14 (66)	40 ± 44 (63)	61 ± 69 (21)	<0.001
TB (mg/dL)	0.4 ± 0.2 (18)	0.4 ± 0.2 (66)	0.5 ± 0.2 (63)	0.5 ± 0.2	0.7825
AP (U/L)	78 ± 22 (18)	82 ± 22 (66)	77 ± 24 (63)	85 ± 37 (21)	0.4098
Alb (g/dL)	3.8 ± 0.3 (18)	3.7 ± 0.4 (66)	3.9 ± 0.4 (63)	3.7 ± 0.6 (21)	0.6879

Data are reported as mean ± SD, with the number of observations in parentheses. The *P* values were generated with the Kruskal-Wallis test.

640,000 individuals in the United States may have cirrhosis secondary to NAFLD.[13] Furthermore, only 1% of patients on transplant waiting lists have NAFLD as their underlying diagnosis.[13] The disparity between the estimates of disease progression and the actual observations may be secondary to the relatively long time that NAFLD requires for progression to cirrhosis.[1] Most patients undergo bariatric surgery at a relatively young age (age, 30–50 years),[16] at which time laboratory or pathologic evidence of NAFLD may be found. The clinical manifestations of NAFLD often do not develop, however, for another decade.[1,13] Given the current state of knowledge, the clinical relevance of NAFLD will continue to evolve.

Other groups have documented steatosis and steatohepatitis in 65%–80% and 2–33%, respectively, of patients undergoing a bariatric procedure with concomitant liver biopsy.[17–19] No cases of cirrhosis were discovered in these reports (<100 patients each). Our rates of steatosis and steatohepatitis (90% and 42%, respectively) were somewhat higher than these rates; the reason for this is unclear. We did not uncover any unsuspected cirrhosis in our 177 patients, which is consistent with the 0.1% incidence described earlier. In general, the vast majority of our patients had some degree of steatosis, but fewer than half had steatohepatitis, and the majority of these cases were mild (i.e., grade 1; see Table 2).

Univariate analysis of factors associated with NAFLD in our patients revealed, not surprisingly, that elevation of AST and/or ALT was associated with both steatosis and steatohepatitis. The degree of transaminase elevation in the typical patient was not dramatic, however; the average transaminase elevation (from a non-normal distribution; see Fig. 1) in a patient with NAFLD was only about twice that of a patient without disease. No other independent variables for disease were found. The lack of a simple relationship between BMI and NASH has been documented by others.[19,20] Our multivariate analysis, however, found an unexpected interaction among age,

Table 4. Correlation of various factors with the grade of steatohepatitis

Variable	Grade of steatohepatitis 0	1	2	*P* value
Age (yr)	40.0 ± 11.4 (102)	41.8 ± 10.5 (59)	37.5 ± 12.3 (16)	0.2968
BMI (kg/m^2)	49.0 ± 8.1 (101)	48.8 ± 9.4 (60)	50.6 ± 8.6 (15)	0.5071
AST (U/L)	20 ± 8 (96)	35 ± 37 (58)	41 ± 46 (14)	<0.001
ALT (U/L)	25 ± 14 (96)	46 ± 55 (58)	54 ± 55 (14)	0.0001
TB (mg/dL)	0.5 ± 0.2 (96)	0.4 ± 0.2 (58)	0.5 ± 0.2 (14)	0.2349
AP (U/L)	78 ± 22 (96)	85 ± 30 (58)	69 ± 16 (14)	0.0806
Alb (g/dL)	3.7 ± 0.4 (96)	3.9 ± 0.4 (58)	3.8 ± 0.6 (14)	0.1627

Data are reported as mean ± SD, with the number of observations in parentheses. The *P* values were generated with the Kruskal-Wallis test. Note that for these analyses, the one patient with grade 3 steatohepatitis was grouped with the grade 2 patients.

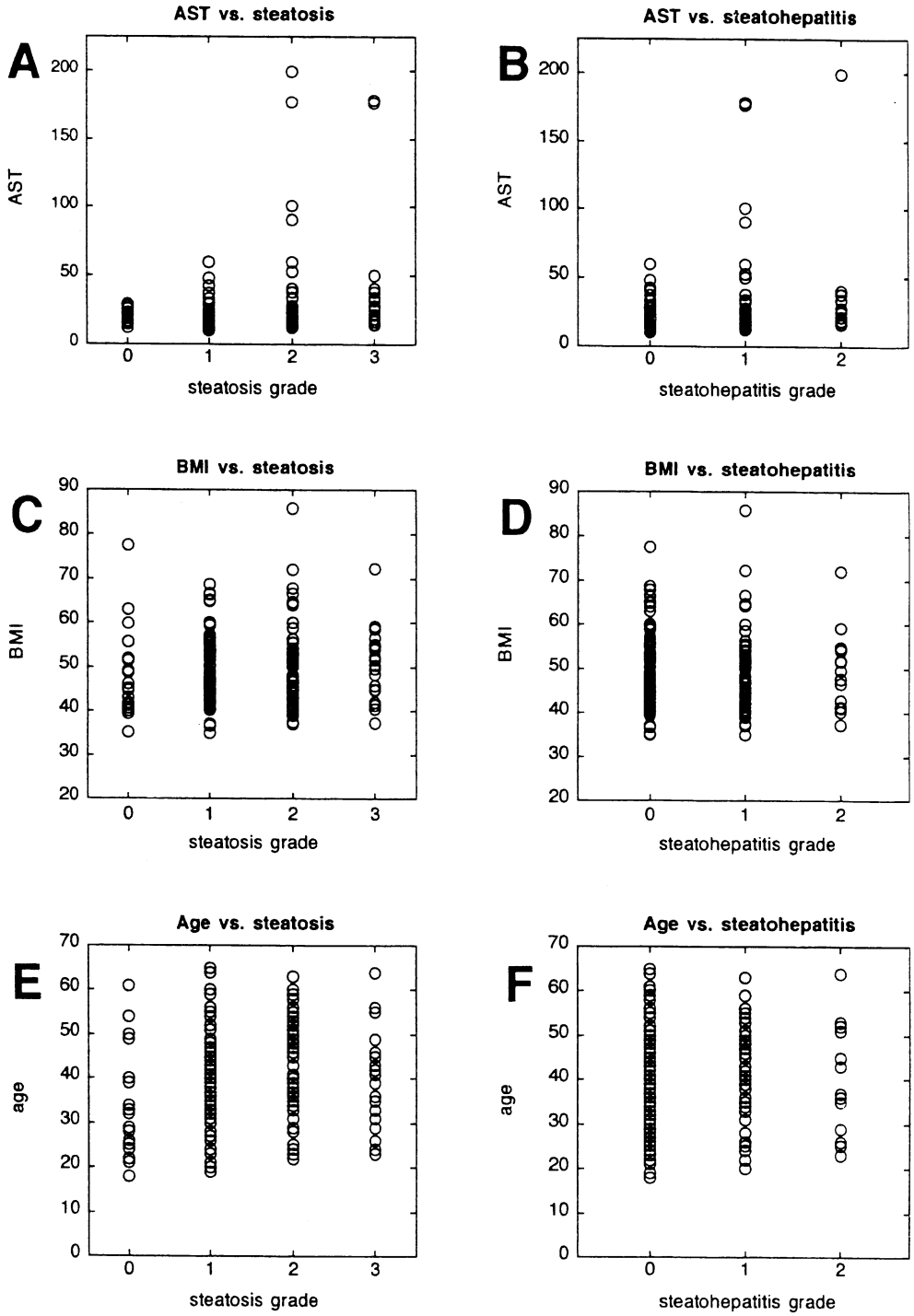

Fig. 1. Raw data plots of single selected variables vs. grade of liver disease. (**A**) Aspartate aminotransferase (AST) vs. grade of steatosis. (**B**) AST vs. grade of steatohepatitis. (**C**) Body mass index (BMI) vs. grade of steatosis. (**D**) BMI vs. grade of steatohepatitis. (**E**) Age vs. grade of steatosis. (**F**) Age vs. grade of steatohepatitis.

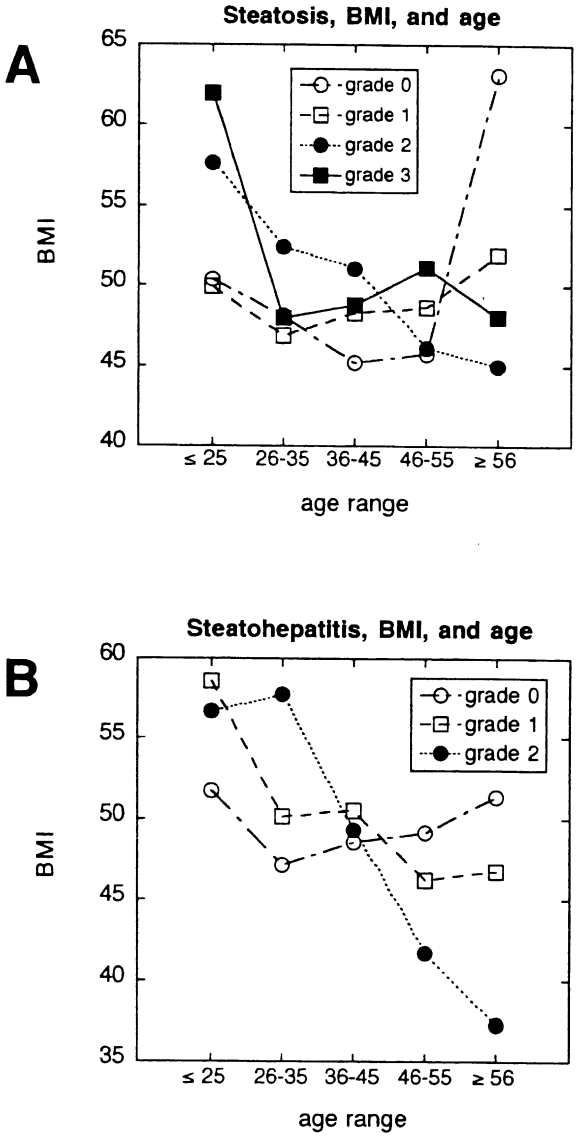

Fig. 2. (**A**) Plot of steatosis grade, body mass index (BMI) and age. For each age range, the mean BMI at each disease grade was plotted; each line represents the relationship between age and BMI at a constant disease grade. (**B**) Similar plot using steatohepatitis grade, BMI, and age.

BMI, and liver disease grade: at younger ages, increasing BMI was associated with both steatosis and steatohepatitis, whereas at older ages, increasing BMI was associated with less disease. In other words, BMI was a positive risk factor for NAFLD in the younger group but a negative risk factor in the older group. This finding seems somewhat counterintuitive, given what is known about the pathophysiology of NAFLD. Furthermore, the clinical implications of this paradoxical effect of BMI are unclear. This finding will need to undergo further examination. The reason that increased BMI may have a protective effect against NASH in older patients is at this point only speculative.

Table 5. Value and 95% confidence intervals for age and body mass index values at which there is a change in the direction of the effect of the other variable

Variable	Steatosis	Steatohepatitis
Age (yr)	45.7 (36.2–55.3)	40.3 (33.8–46.9)
Body mass index (kg/m^2)	54.6 (47.3–62.1)	50.4 (45.1–55.7)

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