CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2006;4:1544–1549

Influence of High Body Mass Index on Outcome in Acute Liver Failure

ANNA RUTHERFORD,* TIM DAVERN,‡ J. EILEEN HAY,§ NATALIE G. MURRAY,¶ TAREK HASSANEIN,|| WILLIAM M. LEE,# and RAYMOND T. CHUNG* FOR THE ACUTE LIVER FAILURE STUDY GROUP

*GI Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ‡Department of Gastroenterology, University of California San Francisco, San Francisco, California; §Mayo Clinic, Rochester, Rochester, Minnesota; ¶Baylor All Saints Transplant Services, Baylor University Medical Center, Fort Worth, Texas; ||University of California San Diego, San Diego, California; and #Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas

Background & Aims: Diabetes and obesity affect development of nonalcoholic fatty liver disease. Nonalcoholic fatty liver disease increases susceptibility to hepatic injury and limits regenerative capacity, which might increase adverse outcomes in acute liver failure. There is no difference in the prevalence of diabetes in acute liver failure patients when compared with the general population, but no large studies have examined the relationship of obesity to incidence or outcome of acute liver failure. **Methods:** Seven hundred eighty-two adult patients with acute liver failure were prospectively enrolled from 1998–2004. Body mass index, history of diabetes, and outcome were recorded. Multivariable logistic regression was used for the analysis. **Results:** Compared with 30.4% of adults in the National Health and Nutrition Examination Survey III, 29.1% of adult patients with acute liver failure were obese ($P = .542$). Obese patients had 1.63 times the odds of transplantation or death as nonobese patients (1.04–2.55, $P = .033$). Severely obese patients had 1.93 times the odds of transplantation or death (1.02–3.62, $P = .042$). There were no differences in the proportion of patients listed for transplantation, with body mass index greater or less than 30, 35, or 40 ($P = .264$, $P = .112$, $P = .244$, respectively). Obese patients had 3.4 times the odds of dying after transplantation (1.29–8.87, $P = .01$). **Conclusions:** Obesity does not appear to be more prevalent in acute liver failure. However, obese and severely obese patients had significantly poorer outcomes when they developed acute liver failure. This difference is not explained by weight discrimination in listing patients for transplantation, despite evidence for poorer post-transplant outcomes.

There is strong evidence for the involvement of diabetes and obesity in the development of nonalcoholic fatty liver disease (NAFLD). NAFLD is a well-described feature of the metabolic syndrome that includes type II diabetes (T2DM), obesity, hypertension, and hyperlipidemia. NAFLD affects 10%–24% of the general population and 58%–75% of the obese population. Diabetes affects 7.8% of the U.S. adult population, and about 50% of patients with diabetes have NAFLD.[1] The combination of diabetes and obesity might pose an added risk; among severely obese patients with diabetes, 100% were found to have at least mild steatosis, 50% had steatohepatitis, and 19% had cirrhosis.[2] Diabetes and obesity are known to be the 2 strongest predictors of fibrosis in NAFLD.[3]

There has been a considerable body of research to examine how steatosis causes liver damage. Both obese patients and patients with T2DM have increased insulin resistance. Insulin normally suppresses lipolysis; therefore, insulin resistance increases circulating levels of free fatty acids, which are taken up by the liver. Increased intrahepatic levels of fatty acids represent a potential source of oxidative stress (free electrons, H_2O_2, and reactive oxygen species) from increased beta oxidation of fatty acids by hepatocyte mitochondria. Oxidative stress also stimulates cytokine production, which can cause hepatocyte injury and inhibit hepatic regeneration. Previous studies in animals and humans with NAFLD have shown that fatty livers are more vulnerable than normal livers to oxidative stress, sudden increases in free fatty acid supply, endotoxin/cytokine-mediated injury, and ischemia or other causes of ATP depletion.[4] Therefore, most obese diabetics have baseline evidence of underlying, clinically silent liver disease, which has been shown to be susceptible to further insults, and to have limited capacity for regeneration,[5,6] both factors that could render persons with NAFLD more susceptible to severe acute liver failure than the average population.

There are 2 studies linking acute liver failure (ALF) with diabetes, not specifically related to drug toxicity.[7,8] A cohort study compared 173,643 veterans with diabetes with 650,620 controls and followed them for the occurrence of ALF during a period of 5 years.[7] After controlling for comorbid disease, age, sex, ethnicity, viral hepatitis, chronic liver disease, and alcoholism, a relative risk of 1.4 for developing ALF was observed among diabetics ($P < .0001$). Davern et al[8] used the Acute Liver Failure Study Group (ALFSG) database to examine the prevalence of diabetes in patients with ALF, comparing this with appropriately matched controls from National Health Interview Survey (NHIS). They found that although the prevalence of diabetes was slightly higher in the ALF patients (5.3%) than in the general United States population (4.8%), the difference was not significant ($P = .565$).

There are no large studies that address the relationship between obesity and the incidence and outcome of ALF. Caldwell and Hespenheide[9] have published the only study linking obesity (body mass index [BMI] >30) with ALF. This was a retrospective description of 5 obese patients with no history of liver disease who presented with liver failure during a 4- to 16-week course and had biopsies suggestive of NAFLD. Four

Abbreviations used in this paper: ALF, acute liver failure; ALFSG, Acute Liver Failure Study Group; BMI, body mass index; MELD, Model for End-stage Liver Disease; NHANES III, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey; NAFLD, nonalcoholic fatty liver disease; T2DM, type II diabetes mellitus.

1542-3565/06/$32.00
doi:10.1016/j.cgh.2006.07.014

patients died of liver failure complicated by multiorgan failure 4–16 weeks after the onset of symptoms, and one underwent successful urgent transplantation.

We hypothesized that obesity is more common in patients with ALF than in appropriate control populations, and that obesity, defined as a BMI ≥30 kg/m^2, and/or a history of diabetes would predict poor outcome in patients with ALF.

Methods

The ALFSG is a National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Disease–funded group of 24 academic centers established in 1998 to better define the epidemiology and outcome of ALF in the U.S. All patients enrolled into the ALFSG study have, by definition, an international normalized ratio >1.5, evidence of hepatic encephalopathy, and an illness of less than 26 weeks with no history of chronic liver disease. Because all subjects are encephalopathic, written informed consent is obtained from legal next of kin. Data are collected on separate admission and outcome case report forms, with outcome defined as liver transplantation, discharge, or death 3 weeks after admission. This study was performed according to the institutional review board guidelines of each of the 24 centers of the ALFSG and the ALFSG ancillary studies committee.

Adult patients with ALF (n = 782) were prospectively identified from January 1, 1998–December 31, 2004, and baseline prospective data were collected on each patient's study center, age, gender, race, height, weight, medical history of diabetes, comorbid illness, Model for End-stage Liver Disease (MELD) score, etiology of ALF, and outcome at 3 weeks after enrollment in the study.

The distribution of BMIs in the ALFSG cohort was compared with a representative gender-adjusted U.S. BMI distribution estimated by the National Health and Nutrition Examination Survey (NHANES III) by using a Fisher exact test.

For the analysis, the primary predictor was obesity (BMI ≥30 vs <30). BMI (kg/m^2) was calculated from weights (kg) and heights (cm) measured on admission to the study. World Health Organization criteria for BMI classification were used: underweight, <18.5; normal, 18.5–24.9; overweight, 25–29.9; obese, 30–34.9; severely obese, 35–39.9; very severely obese, >40. History of diabetes was defined as either mention of diabetes in medical history or at least one oral hypoglycemic medication or long-acting insulin on admission to the study. Comorbid illness was defined by using the Charlson comorbidity index.[10] MELD score was calculated by using the standard equation: $(0.957 \times \ln(\text{creatinine mg/dL}) + 0.378 \times \ln(\text{bilirubin mg/dL}) + 1.120 \times \ln(\text{INR}) + 0.643) \times 10$.

The primary outcome for the analysis was spontaneous survival versus liver transplantation and/or death from ALF.[11,12] We examined 3-week outcomes for this study, because the initial study follow-up for the ALFSG database occurs at 3 weeks after hospitalization, transplantation, or death. In prior studies from this group, 93% of patients had a definitive outcome at 3 weeks.[13]

The patients with BMI recorded in the database had their baseline characteristics compared by outcome, by using Fisher exact and Wilcoxon tests for nonparametric data. The baseline characteristics of the patients with recorded BMI were then compared with those of patients with missing BMI data by using Fisher exact and Wilcoxon tests. In crude analysis, univariate relationships were tested by using logistic regression. To determine whether obesity was related to outcome in ALF after adjusting for all other clinical variables, a multivariable logistic regression model was developed. The predictors included in the model were chosen on the basis of previously published studies of factors known to be predictive of outcome in ALF (etiology, MELD[14]), or predictors that were significant in univariate testing. The outcomes and frequency of listing for transplant for patients with BMI >35 and >40 were examined, as well as post-transplant outcomes. All analyses were performed by using SAS for Windows version 9.1.3 statistical software (SAS Institute Inc, Cary, NC). All analyses were 2-tailed. A *P* value of less than .05 was considered to indicate statistical significance.

Results

Patient Population

Of the 782 adult patients in the ALFSG database, 573 (73.3%) had BMI recorded. Table 1 shows the baseline characteristics of these 573 patients by outcome. The mean BMI for patients who underwent transplantation or died (28.8 ± 8.3 kg/m^2) was significantly greater than that of spontaneous survivors (26.6 ± 7.1 kg/m^2, *P* = .0001). Table 2 shows the baseline characteristics of the 209 missing patients as compared with the patients with BMI recorded. There were no significant differences between these 2 groups. One hundred sixty-seven (29.1%) adult ALF patients were obese, compared with 30.4% of adult Americans in the NHANES III database (*P* = .542).[15]

Table 1. Baseline Demographics of Patients by Outcome

	Spontaneous survival (n = 255)	Death and/or transplant (n = 318)	*P* value
Mean age (*y*)	38.7 ± 13.5	39.8 ± 14.5	.318
% Female	65.5% (167)	66.7% (212)	.790
White	82.1% (206)	71.9% (220)	
African American	9.9% (25)	15.7% (48)	
Hispanic	2.4% (6)	5.2% (16)	.056
Asian	3.9% (10)	5.9% (18)	
Native American	1.6% (4)	1.3% (4)	
History of diabetes	5.9% (15)	6.3% (20)	.863
Mean BMI	26.6 ± 7.1	28.8 ± 8.3	.0001
Charlson comorbidity score			
0	78% (199)	80.5% (256)	
1–2	16.9% (43)	15.4% (49)	
>2	5.1% (13)	4.1% (13)	.736
Mean MELD	28.4 ± 9.9	36.3 ± 9.6	<.0001
Etiology of ALF			
Acetaminophen	64.7% (165)	31.1% (99)	
Drug-induced liver injury	5.5% (14)	15.4% (49)	
Viral hepatitis	9.8% (25)	12.6% (40)	
Indeterminate	9.4% (24)	19.5% (62)	<.0001
Autoimmune hepatitis	2.4% (6)	9.1% (29)	
Acute fatty liver of pregnancy	1.2% (3)	0.3% (1)	
Wilson's disease	0	3.8% (12)	
Other	7.1% (18)	8.2% (26)	

Table 2. Baseline Demographics of People With Missing BMI vs Recorded BMI

	Missing BMI (n = 209)	BMI recorded (n = 573)	*P* value
Mean age (*y*)	40.1 ± 14.1	39.3 ± 14.1	.375
% Female	71.8% (150)	66.1% (379)	.143
White	76.7% (158)	76.5% (426)	
African American	7.8% (16)	13.1% (73)	.057
Hispanic	7.8% (16)	4.0% (22)	
Asian	6.8% (14)	5.0% (28)	
Native American	0.9% (2)	1.4% (8)	
History of diabetes	4.8% (10)	6.1% (35)	.603
Charlson comorbidity score			
0	80.4% (168)	79.4% (455)	.344
1–2	14.3% (30)	16.1% (92)	
>2	5.3% (11)	4.5% (26)	
Mean MELD	31.8 ± 10.1	32.8 ± 10.5	.225
Etiology of ALF			
Acetaminophen	42.1% (88)	46.1% (264)	.519
Drug-induced liver injury	14.8% (31)	11.0% (63)	
Viral hepatitis	11.5% (24)	11.3% (65)	
Autoimmune hepatitis	4.3% (9)	6.1% (35)	
Acute fatty liver of pregnancy	1.4% (3)	0.7% (4)	
Wilson's disease	1.4% (3)	2.1% (12)	
Other	10.5% (22)	7.7% (44)	
Outcome			
Spontaneous survival	43.1% (90)	44.5% (255)	.745
Transplant and/or death	56.9% (119)	55.5% (318)	

Predictors of Outcome in Acute Liver Failure

The significant crude predictors of outcome in ALF include obesity, race, etiology of ALF, and MELD score (Table 3). More obese patients than nonobese patients underwent transplantation or died (67.1% and 50.7%, respectively; *P* = .0004). On the basis of univariate analysis, an obese patient with ALF had 1.98 times the odds (1.36–2.88, *P* = .0004) of undergoing transplantation or dying as compared with someone who was not obese. History of diabetes was not a significant univariate predictor of outcome. As shown in Table 4, even when adjusting for age, sex, race, history of diabetes or other comorbid illness, MELD score, and etiology of ALF, obese patients with ALF had 1.63 times the odds (1.04–2.55, *P* = .033) of undergoing transplantation or dying as compared with nonobese patients. Severely obese patients (BMI ≥35) with ALF had 1.93 times the odds of transplantation or death (1.02–3.62, *P* = .042) compared with patients with BMI <35.

Table 3. Unadjusted Odds of Death and/or Transplant

Predictor	Odds ratio	Confidence interval	*P* value
Obesity (BMI ≥30)	1.98	1.36–2.88	.0004
History of diabetes	1.07	0.54–2.14	.840
Age	1.01	0.99–1.02	.321
Male sex	1.05	0.74–1.49	.767
Charlson score 1–2 vs 0	0.89	0.57–1.39	.597
Charlson score >2 vs 0	0.92	0.71–1.20	.532
African American vs white	1.80	1.07–3.02	.027
Other race[a] vs white	1.78	1.00–3.16	.049
Study center number[b]			.482
MELD	1.09	1.07–1.11	<.0001
Drug-induced vs acetaminophen	4.32	2.29–8.14	<.0001
Indeterminate vs acetaminophen	3.19	1.89–5.37	<.00001
Viral vs acetaminophen	1.97	1.14–3.41	.015
Other etiology[c] vs acetaminophen	1.78	0.94–3.38	.077

[a]Other race includes Native American, Asian, and Hispanic.
[b]This univariate regression was done with a class statement, treating study center as a categorical variable (24 categories). The *P* value presented is the Wald χ^2 *P* value with 23 degrees of freedom.
[c]Other etiology includes shock liver, mushroom toxicity, autoimmune hepatitis, Wilson's disease, acute fatty liver of pregnancy, Budd Chiari syndrome.

Table 4. Adjusted Relationship of BMI to Outcome in ALF

Predictor	Odds ratio	Confidence interval	*P* value
Obesity (BMI ≥30)	1.63	1.04–2.55	.033
Age	0.99	0.98–1.01	.849
Male sex	1.81	1.16–2.80	.008
Charlson score 1–2 vs 0	1.11	0.65–1.92	.704
Charlson score >2 vs 0	0.89	0.65–1.23	.479
African American vs white	1.76	0.94–3.29	.079
Other race[a] vs white	1.93	0.99–3.77	.054
MELD	1.10	1.07–1.12	<.0001
Drug-induced vs acetaminophen	4.85	2.35–10.02	<.0001
Indeterminate vs acetaminophen	3.92	2.08–7.40	<.0001
Viral vs acetaminophen	1.80	0.95–3.41	.073
Other etiology[b] vs acetaminophen	1.47	0.70–3.11	.310

NOTE. To describe the goodness of fit of the final model, the Hosmer-Lemeshow test for the model has a χ^2 value of 9.63 with *P* = .291 with 8 degrees of freedom.
[a]Other race includes Native American, Asian, and Hispanic.
[b]Other etiology includes shock liver, mushroom toxicity, autoimmune hepatitis, Wilson's disease, acute fatty liver of pregnancy, Budd Chiari syndrome.

By separating the outcomes into death and transplantation while still controlling for age, sex, race, history of diabetes and other comorbid illness, MELD score, and etiology of ALF, obese patients with ALF had 1.35 times the odds of dying (0.89–2.06, *P* = .162) and 1.58 times the odds of undergoing transplantation (0.99–2.53, *P* = .055), whereas severely obese ALF patients had 1.26 times the odds of dying (0.72–2.19, *P* = .414) and 1.92 times the odds of undergoing transplantation (1.07–3.47, *P* = .030).

Of the 19 (3.3%) ALF patients who were both obese and diabetic, 63.2% underwent transplantation or died versus 55% of the nonobese, nondiabetics (*P* = .640).

Figure 1 illustrates that as the BMI increases for patients with ALF, when compared with the patient with a normal BMI (18.5–24.9), the odds of dying or undergoing transplantation significantly increases. The overall test for trend had a *P* value of .044.

Obesity and Etiology of Acute Liver Failure

Of all patients with acetaminophen-related ALF, obese patients were significantly under-represented compared with

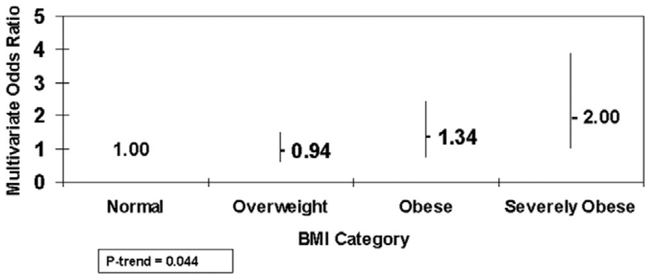

Figure 1. Odds of death or transplantation by increasing BMI. As BMI increases for patients with ALF, when compared with the ALF patient with normal weight (BMI, 18.5–24.9), the odds of dying or undergoing transplantation significantly increases for obese (BMI, 30–34.9) and severely obese (BMI, 35–39.9) ALF patients. The overall test for trend has a *P* value of .044.

nonobese patients, when one would expect the proportion of obese patients to be similar to overall prevalence of obesity in the U.S. population (18.9% vs 81.1%, $P < .00001$). Of all patients with autoimmune hepatitis, obese patients were significantly over-represented compared with nonobese patients (48.6% vs 51.4%, $P = .012$). Obese patients were also significantly over-represented in ALF caused by shock liver, mushroom toxicity, and Budd-Chiari syndrome (45.5% vs 54.6%, $P = .016$) (Figure 2). Of all patients with BMI recorded, acute fatty liver of pregnancy occurred only in obese patients (n = 4).

Obesity and Liver Transplantation

There was no significant difference in the proportion of patients listed for transplant with BMI greater or less than 30 (46.1% vs 40.6%, $P = .264$), BMI greater or less than 35 (50.6% vs 40.9%, $P = .112$), and BMI greater or less than 40 (51.3% vs 41.6%, $P = .244$). Obese patients had 3.4 times the odds of dying after transplantation as nonobese patients (1.29–8.87, $P = .01$).

Discussion

Several recent studies have noted associations between obesity and ALF. Canbay et al[16] retrospectively examined 34 patients with acute and acute-on-chronic liver failure. They found that BMI was significantly higher in acute-on-chronic liver failure than in ALF ($P < .002$). Kanda et al[17] retrospectively examined 31 non-severe acute hepatitis patients, 24 severe acute hepatitis patients, and 14 fulminant hepatitis patients and found that mean BMI was not different between the non-severe and severe/fulminant groups, but that the 2 morbidly obese patients studied both developed more severe liver failure.

With the benefit of the large, prospective ALFSG cohort, this study represents an opportunity to examine BMI trends in a large population with a uniform definition of ALF. Obesity was no more prevalent in this adult ALF population than in a noninstitutionalized adult U.S. population (NHANES III), implying that obesity or underlying NAFLD does not increase the risk of developing ALF itself. However, obesity was at least 60% more likely to be associated with poor outcome in ALF, specifically death or the need for liver transplantation. This relationship holds even when one controls for age, gender, and race, all of which affect the prevalence of obesity, as well as controlling for etiology of ALF, MELD score, and comorbid illness, which affect outcome. Interestingly, diabetes alone and concurrent diabetes and obesity had no further impact on patient outcome in ALF than obesity alone, suggesting that BMI is a more important predictor of outcome than diabetes.

A limitation of this study is that about one fourth of the patients in the database had no BMI recorded. However as shown in Table 2, these patients were very similar to the patients with recorded BMI with respect to outcome and other clinical characteristics. The lack of BMI data recorded in this proportion of patients was likely attributable to the logistically difficult task of measuring BMI, particularly height, in critically ill patients in the intensive care unit. In fact, for the majority of patients with missing BMI, there was no height measurement recorded on the case report form. We were also unable to validate the accuracy of the measurements of height and weight in those who had BMI recorded at any study center or to distinguish whether they were estimates or actual measured values. However, we believe that weights were routinely checked in the intensive care unit setting, and heights were reasonably estimated and not subject to inherent bias.

Surprisingly, the Charlson comorbidity score used to represent a patient's comorbidities was not predictive of outcome in univariate analysis. This could potentially be explained by the fact that patients with ALF tend to be quite young, and the majority had no comorbid illness (80% had a Charlson score of 0), meaning that fewer people with higher Charlson scores might have limited the power of this association. In addition, although male gender was not a significant predictor of outcome in univariate analysis, when controlling for all other factors in the multivariate model, it appeared that male gender

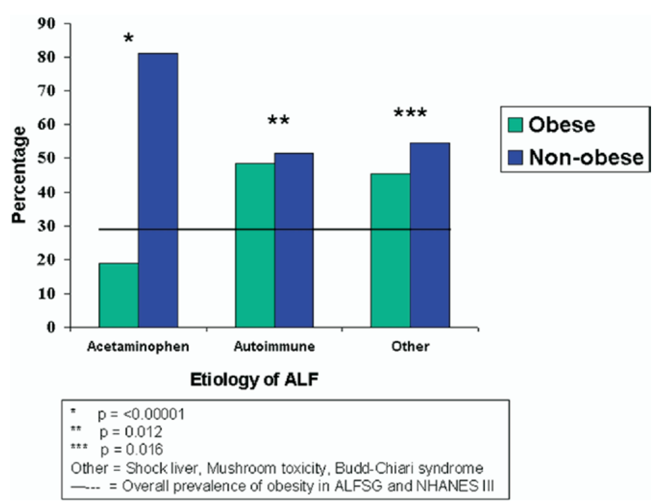

Figure 2. BMI and etiology of ALF. Distribution of etiology of ALF differed significantly between nonobese and obese patients in ALF as a result of acetaminophen, autoimmune hepatitis and shock liver, mushroom toxicity, and Budd-Chiari syndrome. Of all patients with acetaminophen-related ALF, obese patients were significantly under-represented compared with nonobese patients, when one would expect the proportion of obese patients to be similar to overall prevalence of obesity in the U.S. population (18.9% vs 81.1%, $P < .00001$). Of all patients with autoimmune hepatitis, obese patients were significantly over-represented compared with nonobese patients (48.6% vs 51.4%, $P = .012$). Obese patients were also significantly over-represented in ALF caused by shock liver, mushroom toxicity, and Budd-Chiari syndrome (45.5% vs 54.6%, $P = .016$).

is almost twice as likely to predict poor outcome in ALF. In the multivariate model, gender was collinear with MELD, and there was a significant difference in the mean MELD score of men versus women (35.4 ± 9.9 vs 31.5 ± 10.5, $P < .0001$). To our knowledge, there are no prior data showing gender differences in MELD score.

There were significant differences in distribution of the etiologies of ALF between obese and nonobese patients in our study. In particular, the difference in prevalence of ALF caused by acetaminophen between obese and nonobese patients was dramatic, despite similar survival rates in the 2 groups. Whereas these data suggest that obese patients appear to be less susceptible to ALF from acetaminophen, further information regarding the profile of all acetaminophen users would be required to reliably distinguish whether (1) obese patients are less likely to use acetaminophen; or (2) they experience less hepatotoxicity for a given exposure to acetaminophen. In addition, an explanation for the observation that obese patients are less susceptible to ALF from acetaminophen is not known. One study showed that maximal acetaminophen plasma concentrations are reached at significantly later times and are significantly lower in obese patients compared with controls, implying a lower rate of absorption.[18] Also, animal and human studies have shown that the absolute clearance of acetaminophen from plasma is increased in obese subjects, a result of increased formation and clearance of glucuronide and sulfate conjugates.[19] In fact, conjugating capacity has been shown to increase proportionally to total body weight, presumably as a result of increased nutritional stores.[20] It has also been shown that obese Zucker rats possess higher total hepatic glutathione content as a result of greater liver weight.[21] Collectively, decreases in absorption and increases in conjugation and clearance of acetaminophen and its metabolites could explain the observed decreased frequency of ALF caused by acetaminophen in obese patients.

We showed that obese patients with ALF had 3.4 times the odds of dying after transplantation as nonobese patients, which has been previously shown and used as evidence to limit liver transplantation in severely obese patients.[22–24] Interestingly, although there was no significant difference in frequency of listing patients for transplantation on the basis of different BMI, patients with BMI >30, >35, and >40 all trended toward being more frequently listed than patients with BMI below those thresholds. Although there are no uniform criteria for listing for transplantation in ALF, all centers in the ALFSG listed ALF patients if they experienced clinical worsening and had no contraindications to transplantation. Although these are not strict or measurable criteria for listing, we believe they are not inherently biased, or that the decision to list a patient is not drawn from the prognostic variables uncovered in this study. Therefore, we believe that our findings reflect not only the lack of discrimination in listing obese patients for transplantation but also the fact that obese patients with ALF tend to do more poorly and are therefore more frequently listed for transplantation.

In summary, obesity does not appear to be more prevalent in ALF than in a representative sample of the U.S. noninstitutionalized, civilian population. However, obese and morbidly obese patients had significantly poorer outcomes in ALF, even when controlling for age, gender, race, comorbid illness, MELD score, and etiology of ALF. This difference is also not explained by weight discrimination in listing patients for transplantation. Diabetes did not post a significant additive risk for poor outcome for obese patients. In addition to MELD and etiology of ALF, obesity appears to be a powerful clinical marker of poor outcome in ALF, and the inclusion of BMI in future prognostic models for ALF appears to be warranted.

Appendix

U.S. Acute Liver Failure Study Group, 1998–2006: William M. Lee (Principal Investigator), Julie Polson, Linda Hynan, Joan Reisch, Carla Pezzia, Joe Webster, University of Texas Southwestern Medical Center, Dallas, Texas; Anne Larson, University of Washington, Seattle, Washington; Tim Davern, University of California, San Francisco, California; Paul Martin, Mount Sinai School of Medicine, New York, New York; Timothy Macashland, University of Nebraska, Omaha, Nebraska; J. Eileen Hay, Mayo Clinic, Rochester, Minnesota; Natalie G. Murray, Baylor University Medical Center, Dallas, Texas; Obaid Shakil Shaikh, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Andres Blei, Northwestern University Medical School, Chicago, Illinois; Kenneth Ingram, Atif Zaman, Oregon Health Sciences University, Portland, Oregon; Steven Han, University of California, Los Angeles, California; Robert Fontana, University of Michigan Medical Center, Ann Arbor, Michigan; Brendan Mcguire, University of Alabama at Birmingham, Birmingham, Alabama; Raymond T. Chung, Anna Rutherford, Massachusetts General Hospital, Boston, Massachusetts; Alastair Smith, Duke University Medical, Durham, North Carolina; Michael L. Schilsky, New York Presbyterian Hospital, New York, New York; Adrian Reuben, Medical University of South Carolina; Andres Riera, Santiago Munoz, Albert Einstein Medical Center, Philadelphia, Pennsylvania; Mical Campbell, Rajender Reddy, University of Pennsylvania, Philadelphia, Pennsylvania; Todd Stravitz, Virginia Commonwealth University, Richmond, Virginia; Lorenzo Rossaro, University of California, Davis, California; Raj Satyanarayana, Mayo Clinic, Jacksonville, Jacksonville, Florida; Tarek Hassanein, University of California San Diego, San Diego, California.

References

1. Gupte P, Amarapurkar D, Agal S, et al. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. J Gastroenterol Hepatol 2004; 19:854–858.
2. Silverman JF, Pories WT, Caro JF. Liver pathology in diabetes mellitus and morbid obesity: clinical, pathological and biochemical considerations. Pathol Annu 1989;24:275–302.
3. Angulo P, Keach JC, Batts KP, et al. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology 1999;30:1356–1362.
4. Day CP. NASH-related liver failure: one hit too many? Gastroenterology 2002;97:1872–1874.
5. Leclercq IA, Field J, Farrell GC. Leptin-specific mechanisms for impaired liver regeneration in ob/ob mice after toxic injury. Gastroenterology 2003;124:1451–1464.
6. Reid AE. Nonalcoholic steatohepatitis. Gastroenterology 2001; 121:710–723.
7. El-Serag HB, Everhart JE. Diabetes increases the risk of acute hepatic failure. Gastroenterology 2002;122:1822–1828.
8. Davern TJ, Schilsky ML, Hynan LS, et al. Prevalence of diabetes mellitus in not increased in acute liver failure. Hepatology 2004; 40:499A.
9. Caldwell SH, Hespenheide EE. Subacute liver failure in obese women. Am J Gastroenterol 2002;97:2058–2062.

10. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;5:373–383.
11. Wai CT, Fontana RJ, Polson J, et al. Clinical outcome and virologic characteristics of hepatitis B-related acute liver failure in the United States. J Viral Hepat 2005;12:192–198.
12. Schiodt F, Rossaro L, Stravitz RT, et al. Gc-globulin and prognosis in acute liver failure. Liver Transpl 2005;11:1223–1227.
13. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947–954.
14. Wiesner RH. MELD/PELD and the allocation of deceased donor livers for status 1 recipients with acute fulminant hepatic failure, primary nonfunction, hepatic artery thrombosis, and acute Wilson's disease. Liver Transpl 2004;10(Suppl 2):S17–S22.
15. Hedley AA, Ogden CL, Johnson CL, et al. Prevalence of overweight and obesity among US children, adolescents and adults, 1999–2002. JAMA 2004;291:2847–2850.
16. Canbay A, Chen SY, Gieseler RK, et al. Overweight patients are more susceptible for acute liver failure. Hepatogastroenterology 2005;65:1516–1520.
17. Kanda T, Yokosuka O, Hiraide A, et al. Prevalence of obesity in patients with acute hepatitis: is severe obesity a risk factor for fulminant hepatitis in Japan? Hepatogastroeneterology 2005;52:180–182.
18. Lee WH, Kramer WG, Granville GE. The effect of obesity on acetaminophen pharmacokinetics in man. J Clin Pharmacol 1981;21:284–287.
19. Wong BK, U SW, Corcoran GB. An overfed rat model that reproduces acetaminophen disposition in obese humans. Drug Metab Dispos 1986;14:674–679.
20. Abernethy DR, Greenblatt DJ, Divoll M, et al. Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. J Lab Clin Med 1983;101:873–880.
21. Chaudhary IP, Tuntaterdtum S, McNamara PJ, et al. Effect of genetic obesity and phenobarbital treatment on the hepatic conjugation pathways. J Pharmacol Exp Ther 1993;265:1333–1338.
22. Rustgi VK, Marino G, Rustgi S, et al. Impact of body mass index on graft failure and overall survival following liver transplant. Clin Transplant 2004;18:634–637.
23. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. Hepatology 2002;35:105–109.
24. Pelletier SJ, Maraschio MA, Schaubel DE, et al. Survival benefit of kidney and liver transplantation for obese patients on the waiting list. Clin Transpl 2003;77–88.

Address requests for reprints to: Raymond T. Chung, MD, GI Unit, GRJ 825, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114. e-mail: RTChung@partners.org; fax: (617) 726-5895.

Supported by NIDDK 2 U01 DK058369, which was previously NIDDK R01 DK058369.

The authors thank the ALFSG site coordinators and nurses for their support.