

Editorial

Liver Biopsy at the Time of Bariatric Surgery: A Benefit for Patients and the Medical Community

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The growth of the field of hepatology over the past 30 years has largely been driven by the burgeoning incidences and prevalences of two diseases: hepatitis C and nonalcoholic fatty liver disease (NAFLD). This issue of the *Seminars in Liver Disease*, guest-edited by Professor Jean-Michel Pawlotsky, is devoted principally to the recent explosion of knowledge about the biology of the hepatitis C virus (HCV) and the resulting appearance of multiple new drugs that dramatically increase the success of HCV treatment. In addition, an editor's choice article from the Longitudinal Assessment of Bariatric Surgery (LABS) Consortium raises important questions about NAFLD.

NAFLD is a common and potentially life-threatening obesity-related comorbidity. Nonalcoholic steatohepatitis (NASH), one component of the widely accepted NAFLD spectrum, may be the most common form of chronic hepatitis in the United States, and has been projected to replace hepatitis C–related liver disease as the leading indication for liver transplant.^{1,2} Bariatric surgery (BS) patients are among the highest risk population for NAFLD, which affects up to 98% of patients in some series, and the possible use of BS as a therapeutic approach to treat NAFLD is gaining attention.³ However, the natural history of NAFLD in BS patients and the impact of BS on NAFLD disease progression remain incompletely described. The depth of our uncertainty about key aspects of fatty liver disease is reflected in recent publications challenging the basic concepts that simple hepatic steatosis is part of the broader spectrum that includes NASH, NASH with fibrosis, and cirrhosis,⁴ or that the proportion of total liver transplants going to patients with fatty liver disease is significantly increasing.⁵

In this issue of the *Seminars in Liver Disease*, Kleiner and colleagues⁶ report histologic findings from intraoperative liver biopsies in a subset of patients in the LABS study cohort. While biopsies were not performed universally or in an unbiased manner, the burden of liver disease in this population was predictably high, with borderline or definitive NASH

found in over a third of biopsied patients and bridging fibrosis or cirrhosis in 4.2%. Perhaps most striking was that among patients with alanine aminotransferase (ALT) < 35 IU/L, a widely accepted upper limit of normal, 24% had borderline or definitive steatohepatitis, 6.4% had a NAFLD activity score (NAS) \geq 5, and 2% had bridging fibrosis or cirrhosis. When even more stringent ALT criteria were used (normal: < 30 IU/L for men and < 19 IU/L for women),⁷ 19% had borderline or definitive steatohepatitis, 3.7% had NAS \geq 5, and 1.6% had bridging fibrosis or cirrhosis, rendering even these cutoffs for ALT inadequate to exclude clinically important liver disease in these very high-risk patients. The authors then used logistic regression modeling as a crude indicator of how much liver disease may have gone undiagnosed in the patients who were not biopsied; the models suggested that almost 6% of unbiopsied patients have bridging fibrosis or cirrhosis and almost half of the patients have borderline or definitive steatohepatitis. As visual inspection of the liver by the surgeon in the operating room may be insufficiently sensitive to detect significant hepatic pathology, much of the important liver disease in the cohort remains undiagnosed.

This report reminds us of just how little we know about the burden of liver disease in the BS population, and perhaps supports the growing sentiment that liver biopsy at the time of BS should be universally considered. Several lines of evidence support the fact that a clearer understanding of the liver histology in BS patients will benefit both individual patients and the medical community.

NAFLD Diagnosis and Staging Is an Important Goal

The diagnosis of steatohepatitis and/or advanced fibrosis in the setting of fatty liver infiltration has important prognostic and therapeutic implications for patients. It is clear that advanced

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fibrosis is the histologic finding most predictive of overall and liver-related mortality among patients with NAFLD,⁸⁻¹⁰ and liver enzymes are not sensitive or specific indicators of advanced fibrosis (as detailed later). The identification of patients with advanced fibrosis is key to the prevention of life-threatening complications including hepatocellular carcinoma (HCC) and/or decompensated end-stage liver disease. It is also clear that patients with NASH have a worse prognosis than those with simple steatosis. Patients with obesity-associated NASH are at risk for fibrosis progression with the development of cirrhosis in 20% to 40% of cases, and thus a subsequent risk of hepatic decompensation and HCC. Patients with NASH also have increased liver- and cardiovascular-related mortality compared with matched controls without NAFLD or NAFLD without associated steatohepatitis.¹¹⁻¹³

In addition to informing prognosis and the need for screening, the identification of NAFLD and/or NASH may provide an opportunity to alter the natural history of disease. While currently recommended therapies are limited to life style modifications, control of metabolic syndrome manifestations, and limited pharmacologic interventions such as vitamin E and pioglitazone in subsets of patients with biopsy-proven disease, treatment approaches for this increasingly prevalent disease are rapidly evolving.^{3,14} Without knowledge of their chronic liver disease, BS patients with NAFLD and their care providers will increasingly miss important opportunities to halt or slow disease progression. There is an important analogy to hepatitis C, which will remain a major clinical problem for decades despite the new availability of curative treatments because the vast majority of infected individuals worldwide are unaware that they are infected and will not present for treatment until their disease is advanced and symptomatic.

Liver Disease Negatively Impacts Bariatric Surgery Postoperative Outcomes

While the rates of hepatic decompensation after BS are low overall, it is clear that cirrhosis negatively impacts multiple important patient outcomes including mortality, and that postoperative liver-related deaths do occur.^{15,16} In a recent evaluation of the Nationwide Inpatient Sample dataset between 1998 and 2007, ICD-9 codes were used to compare BS outcomes in patients with (1) no evidence of liver disease, (2) compensated liver disease, and (3) decompensated liver disease (with ascites and/or variceal bleeding).¹⁶ Compensated (odds ratio [OR], 2.2) and decompensated (OR, 21.1) cirrhosis were highly significantly predictive of in-hospital mortality in multivariable modeling controlling for age, demographics, insurance status, and hospital features including surgical volume.

In addition, there is evidence that lesser degrees of liver disease may also predict short-term mortality. Benotti and colleagues recently reported outcomes from more than 150,000 patients in the Bariatric Outcome Longitudinal Database. Evidence of liver disease was significantly associated with 30-day mortality after gastric bypass.¹⁷ In multivariable modeling controlling for body mass index (BMI), age, gender, and cardiopulmonary disease, patients with liver disease

were more than twice as likely to die in 30 days compared with those without liver disease (OR, 2.26; 95% confidence interval, 1.08–4.87). Although these authors used a fairly liberal definition of liver disease including assessment of liver enzymes, imaging, and histologic characteristics to capture patients with a spectrum of NAFLD, liver disease was likely underdiagnosed given the reported prevalence of only 2.4%. The impact of liver disease on long-term surgical outcomes and a more precise understanding of how to risk stratify BS patients with advanced liver disease are important questions that require additional investigation.

Liver Disease in BS Patients Has Been Incompletely Described and Noninvasive Testing Remains Inadequate

While it is clear that NAFLD is common in BS patients, the distribution of each stage (i.e., steatosis, NASH and/or advanced fibrosis, and cirrhosis) and whether there is a consistent pattern of transition between stages to inform prognosis remains uncertain. There are few large studies of BS patients with unbiased biopsy data on which to even make firm statements of prevalence.^{18,19} The most comprehensive prevalence assessment comes from a recent meta-analysis of 12 studies with 1,620 patients who were consecutively biopsied at the time of BS throughout the world.¹⁸ The prevalence of NASH ranged from 24% to 98%, and cirrhosis from 0% to 7%. There are also a limited number of large series of consecutive patients undergoing BS who had intraoperative liver biopsies. In one recent series of 679 patients, 34% of the patients had NASH, and 7% had cirrhosis.²⁰ Interestingly, stage ≥ 2 fibrosis was found in 3% of patients without NAFLD, 18% of patients with simple steatosis, and 50% of patients with NASH, indicating that significant fibrotic liver disease may exist in the absence of ongoing inflammation. While risk factors for significant liver pathology in the setting of BS such as diabetes, hyperlipidemia, and geographic location (hinting at other genetic and environmental influences) have been identified,^{18,21,22} none of these can be used alone to accurately predict liver pathology in an individual patient.

Given the important limitations of liver biopsy, including sampling error and the procedure-related morbidity and mortality, there is great interest in replacing biopsy with noninvasive radiographic or serologic testing. To replace the information obtained by histology, noninvasive testing must quantify hepatic fat, differentiate NASH from simple steatosis, and accurately determine fibrosis stage. Unfortunately, there is currently no sufficiently accurate noninvasive tool that can provide this breadth of information. Basic serologic markers of liver injury such as ALT may statistically correlate with hepatic inflammation, but ALT is not sensitive or specific enough to reliably exclude important liver disease. There is clearly a significant burden of NAFLD, NASH, and fibrosis in patients with normal ALTs in the general population²³⁻²⁵ and in BS patients.¹⁸ Even when conservative ALT cutoffs are used (< 19 IU/L for women and < 30 IU/L for men), significant pathology is not excluded.^{6,25} Thus, a normal ALT cannot be used to justify refraining from performing a liver biopsy at the time of BS.

Several serologic panels have been developed to quantify hepatic fat (e.g., SteatoTest [BioPredictive, Paris, France],²⁶ the fatty liver index,²⁷ the lipid accumulation product,²⁸ and the NAFLD liver fat score²⁹), and perhaps, more importantly, differentiate NASH from simple steatosis (e.g., NashTest [BioPredictive],^{30,31} cytokeratin-18,^{32,33} and other clinical and laboratory algorithms^{34,35}).³⁶ However, the accuracy of these assays vary significantly between NAFLD cohorts, including BS patients,^{31,36,37} and combinations of biomarkers may be required.³⁸ Serologic determinates of fibrosis are perhaps of the greatest clinical significance, and several assays have been designed for and/or tested in NAFLD patients specifically. Panels such as the BARD score,³⁹ the FIB-4 index,⁴⁰ and the NAFLD fibrosis score⁴¹ have been compared in several series, but remain limited by only modest positive and negative predictive values.^{42,43} Among the most commonly referenced is the NAFLD fibrosis score; however, when it was specifically applied to a BS population, only approximately 40% of patients in the tested cohort could have reasonably avoided a liver biopsy and still had a fairly accurate assessment of fibrosis based on the test result.⁴⁴ Thus, despite the large number of assays available, there is currently no serologic test that can replace the information obtained with liver biopsy.

Radiographic methods are also now commonly used to assess steatosis and fibrosis. Ultrasound is a widely available technique to detect hepatic fat, though traditional ultrasound is unable to *quantify* fatty infiltration and its sensitivity is lower in patients with < 30% fat and/or with morbid obesity.⁴⁵ Additional ultrasonographic tools such as the controlled attenuation parameter⁴⁶ and various magnetic resonance (MR) techniques such as chemical shift MR and MR spectroscopy^{47,48} may be among the most sensitive techniques to identify and quantify hepatic fat,^{47,48} but are expensive and/or rarely used clinically. Liver stiffness, as a measure of hepatic fibrosis, can now be assessed with ultrasound or MR elastography, which may be more predictive of advanced fibrosis than serologic markers in this setting.^{49,50} Ultrasound elastography, which was recently approved only in the United States, is the most widely available of these techniques, but has not been extensively tested in the BS population and may not perform as well in the NAFLD population as it does for patients with chronic hepatitis C due to the degree of subcutaneous fat in obese subjects.^{51,52} While imaging techniques will continue to improve and may eventually be the superior approach to quantifying total hepatic fat and/or fibrosis given the sampling error that may occur with biopsy, the major limitation of all available radiographic approaches to date is their inability to detect inflammation, a crucial precursor to the development of progressive disease, including fibrosis.

Impact of Bariatric Surgery on the Natural History of NAFLD Is Not Known

BS has been shown in case-control studies to be associated with a wide variety of significant health benefits including a decrease in all-cause mortality, mortality related to cardiovascular disease, diabetes and cancer, improvement in type 2

diabetes, and improved health-related quality of life.^{53–59} However, despite the fact that the overwhelming majority of BS patients have NAFLD as an obesity-related complication, the impact of BS on the natural history of NAFLD in these patients is unclear. There are no randomized controlled trials that evaluate NAFLD progression, and in the observational data available, follow-up liver biopsies are generally done at variable intervals and only in selected patients. In a recent Cochrane Database Systematic Review, the authors could only conclude that the lack of randomized clinical trial data precluded assessment of the impact of BS on NASH.⁶⁰

There were 21 additional cohort studies included in this Cochrane review,⁶⁰ and studies of BS cohorts with paired liver biopsies have also been compiled in several recent reviews.^{61–64} The vast majority of these studies report reductions in steatosis and lobular inflammation in follow-up compared with intraoperative biopsies, although conclusions about the impact on fibrosis progression are less clear, with several large reports documenting progressive disease.^{19,65} In one of the large prospective cohorts with protocolized liver biopsies 1 and 5 years after BS, the proportion of patients with steatosis and NASH decreased during follow-up; however, fibrosis progression occurred in some patients and the overall mean fibrosis stage increased.⁶⁵ With the variable and generally short-term follow-up of these cohorts, and without a control group of patients who did not undergo BS for comparison, it is difficult to infer the impact of BS on the natural history of NAFLD. There are no large studies with follow-up biopsies over a 5–10 year span after BS that can define the rate of progression between stages in the patients who do or do not lose weight after surgery.

Furthermore, it remains uncertain whether the particular bariatric operation chosen has a significant impact on hepatic effects. It is important to remember that early BS approaches such as jejunioileal bypass frequently resulted in worsening of liver pathology, including reports of precipitating acute liver failure resulting in liver transplant or death.^{66–73} While this procedure is no longer performed, liver failure requiring transplant has also been reported following biliopancreatic diversion, and patients with early *rapid* weight loss, low albumin levels, and excessive malabsorption and malnutrition may be at particular risk of hepatotoxicity in this setting.^{73–77} In fact, weight loss of greater than 1.6 kg/week has been associated with *increased* risk of portal fibrosis.⁷⁸ Thus, the rate of weight loss from any BS approach should be carefully monitored, especially in patients with advanced liver disease. Finally, it is also unknown how manipulation of the hormonal control of weight through various operative approaches and resultant anatomical rearrangements may impact the pathophysiology of NAFLD, though there is emerging evidence that gut peptides such as leptin, ghrelin, glucagon-like peptide-1, and peptide YY play an important role in NAFLD.^{62,63} Additional work is needed to determine whether targeted alteration of these peptide levels may lead to optimization of the surgical approach in patients with NAFLD.

Thus, while BS *may* be an important tool in the treatment of NASH and NAFLD-related fibrosis, as it is for other obesity-related comorbidities, no studies are yet available to confirm

this hypothesis. Despite growing clinical enthusiasm for BS for this indication and the cautious recommendations by some³ to proceed with BS when other measures have failed, given the lack of high-quality studies on the topic, the recently released multisociety practice guidelines on the management of NAFLD¹⁴ appropriately included the following recommendations: “(1) Foregut BS is *not contraindicated* in otherwise eligible obese individuals with NAFLD and NASH (but without established cirrhosis); (2) The type, safety and efficacy of foregut BS in otherwise eligible individuals with established cirrhosis caused by NAFLD are not established; (3) It is premature to consider foregut BS as an established option specifically to treat NASH.” The lack of clinical trial data on the impact of BS on liver-related mortality may be in part due to the large numbers of patients and the relatively long follow-up needed to observe progression of liver disease and liver-related patient outcomes. Important causes of death among NAFLD patients including cardiovascular disease and cancer must also be considered in this context, and registry data may be a more realistic tool in the evaluation of the impact of BS on liver-related mortality. However, clinical trials with pre-determined protocol liver biopsies are clearly needed.

Finally, understanding the impact of BS specifically on patients with NAFLD-related cirrhosis and indications for liver transplant is also increasingly important. Because of the increased operative risks associated with obesity, many transplant centers have BMI cutoffs above which they will not consider liver transplantation. BS has thus been performed in select patients not only to achieve weight loss but also to render individuals acceptable candidates for life saving liver transplant.^{79,80} In the few series reported, there have been small numbers of liver-related deaths and at least one case in which the Roux-en-Y gastric bypass was reversed due to severe malnutrition.⁷⁹ It is unknown whether BS-associated weight loss may provide an additional benefit of disease stabilization or recompensation in select patients.

Future Directions: An Important Opportunity to Study NAFLD Pathogenesis

While thousands of patients have undergone BS worldwide, the overwhelming majority of who have NAFLD, there remain significant holes in our understanding of NAFLD in BS patients, including robust prevalence data and the impact of BS on the natural history of the disease. Although cardiovascular disease and diabetes-related complications of obesity have been well studied in BS patients, liver disease remains an under-recognized epidemic in this population.

While liver biopsy has definite limitations in terms of sampling error and the potential for complications, until noninvasive tests are available that can accurately stage fibrosis, differentiate NASH from simple steatosis, and quantify hepatic fatty infiltration, liver biopsy will remain central to the management of these patients. Despite the lack of highly accurate noninvasive markers, the current clinical guidelines do not recommend liver biopsy except in select patients, including those “with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis.”¹⁴ In

addition, their recommendations on the safety and efficacy of BS in this population are contingent upon whether the patient has cirrhosis, which requires accurate assessment of fibrosis stage. BS patients are among those at the highest risk of NAFLD and its complications, and perioperative risk stratification through accurate staging of disease is crucial in avoiding potentially fatal consequences including liver failure. Thus, liver biopsy in this setting, either before BS in patients with clear evidence of advanced liver disease and/or any signs of portal hypertension or at the time of BS in the remaining patients, is an important part of patient management. One unresolved issue in this regard is the relative safety of liver biopsy as a preoperative versus a laparoscopic intraoperative procedure. While NAFLD-specific treatment options remain limited at this time,¹⁴ important management issues in those with advanced liver disease, including modifying risk factors for disease progression and cardiovascular complications, and screening for HCC and portal hypertension, are crucial goals. As treatment options for patients with NAFLD inevitably improve, just as they finally have for HCV, more aggressive measures to diagnose and stage NAFLD will clearly be indicated and will likely be implemented.

In addition to these benefits to individual patients, accurate characterization of liver histology during BS and subsequently over time may represent an important opportunity to study the pathophysiology of this very complex disease. Coupled with genome-wide association data, such long-term studies may well provide very valuable information about the role of genetics in defining the evolution of NAFLD toward cirrhosis.⁸¹ Careful examination of the differential impact of specific BS procedures on gut peptides and the evolution of liver disease may offer additional important insights. As the prevalence of obesity and thus the need for BS continues to rise, and NAFLD emerges as a leading indication for liver transplant, liver assessment through biopsy (currently the standard) or eventually through noninvasive markers in BS patients will provide invaluable information for both patients and the field of hepatology. Thus, the recommendation by the LABS Consortium that “consideration should be given to routine liver biopsy during BS and medical follow-up of significant hepatic pathology” is a significant positive step.

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