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ASMBS Position Statement on the Impact of Metabolic and Bariatric Surgery on Nonalcoholic Steatohepatitis

Guilherme S. Mazzini, M.D., Ph.D.[a], Toms Augustin, M.D., M.P.H.[b], Sabrena Noria, M.D., Ph.D.[c], Carlos Romero-Marrero, M.D.[d], Na Li, M.D., Ph.D.[e], Bilal Hameed, M.D.[f], Dan Eisenberg, M.D., M.S.[g], Dan E. Azagury, M.D., F.A.C.S.[h], Sayeed Ikramuddin, M.D., M.H.A.[i,*]

[a]*Division of Bariatric and Gastrointestinal Surgery, Department of Surgery, Virginia Commonwealth University, Richmond, Virginia*
[b]*Department of General Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, Ohio*
[c]*Department of Surgery, Division of General and Gastrointestinal Surgery, The Ohio state University, Wexner Medical Center, Columbus, Ohio*
[d]*South Florida Transplant Center, Broward Health Medical Center, Fort Lauderdale, Florida*
[e]*Division of Gastroenterology, Hepatology, & Nutrition, Ohio State University Wexner Medical Center, Columbus, Ohio*
[f]*Department of Medicine, University of California, San Francisco, California*
[g]*Department of Surgery, Stanford University School of Medicine, Stanford, California*
[h]*Section of Minimally Invasive & Bariatric Surgery, Stanford University School of Medicine, Stanford, California*
[i]*Department of Surgery, University of Minnesota, Minneapolis, Minnesota*

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The following position statement is issued by the American Society for Metabolic and Bariatric Surgery in response to inquiries made to the Society by patients, physicians, society members, hospitals, health insurance payors, the media, and others regarding the impact of metabolic and bariatric surgery (MBS) on nonalcoholic fatty liver disease (NAFLD), specifically for laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG). The general principles described here may also apply to other procedures; however, the paucity of procedure-specific literature limits the value of this statement beyond these procedures. Additionally, this statement will mainly focus on , nonalcoholic steatohepatitis (NASH), which is the more severe presentation of NAFLD, strongly associated with type 2 diabetes (T2D), that can lead to fibrosis, cirrhosis, end-stage liver disease, and hepatocellular carcinoma [1,2]. Children and adolescents with obesity undergoing MBS may have unique considerations and are not specifically addressed in this position statement. This statement and its recommendations are based on current clinical knowledge, expert opinion, and published peer-reviewed scientific evidence available at this time. The statement is not intended and should not be taken as a local, regional, or national standard of care. The statement will be revised in the future as additional evidence become available.

Background

NAFLD is one of the most commonly encountered liver disorders worldwide and is strongly connected to the epidemic of obesity [3]. The association with insulin resistance, metabolic syndrome, and T2D is so remarkable that a recent consensus proposed to modify its nomenclature to metabolic associated fatty liver disease (MAFLD), in the presence of metabolic dysregulation [4]. This association is also responsible for the increased cardiovascular risk of patients with NAFLD [5]. NASH is the inflammatory subtype of NAFLD, with histologic demonstration of steatosis in the setting of hepatocyte injury (ballooning) and inflammation, with or without fibrosis. NASH drives the development of liver fibrosis, setting the stage for liver-related

Guilherme S. Mazzini and Toms Augustin have shared first authorship.
* Correspondence: Sayeed Ikramuddin, M.D., M.H.A., Mayo Mail Code 195, 420 Delaware St SE, Department of Surgery, University of Minnesota, Minneapolis, MN 55455
E-mail address: ikram001@umn.edu (S. Ikramuddin).

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complications, with more than 20% of NASH patients developing cirrhosis in their lifetime, as well as an increased risk of hepatocellular carcinoma [2]. NASH has become a burden to the health system, with US$222 billion estimated direct medical costs in the United States in 2017, and the second-leading indication for liver transplant listing in the United States [6,7]. The development of liver fibrosis, with significant fibrosis defined as stage 2 or greater, is also associated with an increased risk of liver-related and all-cause mortality [8]. Therefore, the population in greatest need of therapeutic interventions are those with NASH with significant fibrosis. However, despite considerable developmental efforts targeting inflammatory and fibrotic pathways in clinical trials, there is no drug treatment for NASH that has been approved by the US Food and Drug Administration (FDA).

While there are ethnic and genetic associations that increase susceptibility to NASH [3,9], obesity is the underpinning of the disease, with weight loss being prioritized as first-line therapy [10]. Weight loss through lifestyle intervention often, but not always, leads to resolution of NASH in a dose-dependent fashion [11]. The challenges for weight loss and its maintenance are well recognized, especially in patients with severe obesity, raising the question of the role of MBS in managing patients with NASH. The indication for MBS as a formal treatment for NASH is still a matter of debate, since there are no current randomized controlled trials comparing the effect of MBS and standard clinical care on NASH resolution or fibrosis progression. However, evidence from observational studies [12] have demonstrated a significantly positive impact of MBS on liver histology, NASH resolution, and fibrosis regression.

In this statement, we review the definitions of and diagnostic criteria for NAFLD and NASH and summarize the currently available scientific literature evaluating the impact of MBS on patients with biopsy proven NAFLD and NASH. Beyond this, fundamentally there are 3 questions to be addressed in this statement:

1. What is the impact of both LSG and LRYGB on established endpoints in the management of NASH (resolution of NASH without worsening fibrosis/reduction of fibrosis without worsening NASH)?
2. What is the level of evidence supporting either the LSG or LRYGB as first-line therapy for the treatment of NASH?
3. What is the role of additional screening and/or liver biopsy to identify patients being considered for MBS that are at greater risk of advanced hepatic fibrosis?

The statement has been divided into the following 4sections:

1. Review of the definitions and standards for diagnosis, evaluation, screening, and management of NAFLD
2. Review of literature on the effect of MBS on NAFLD activity score (NAS) and fibrosis score (NFS), in studies with paired liver biopsies
3. Conclusions
4. Recommendations based on level of evidence

Methods

For section 1, a review of the most up-to-date available literature and guidelines was done, summarizing definitions and standards for diagnosis, evaluation, screening, and management of NAFLD and NASH.

For section 2, a review of the literature was done, looking for studies showing the effect of LSG and RYGB on NAS features and NFS, with paired liver biopsies at baseline and follow-up. An electronic Medline literature search for articles with baseline and follow-up liver biopsies from patients undergoing bariatric surgery, published between January 2005 and January 2021, was performed. Key terms used were “bariatric surgery,” “bypass,” “sleeve,” “liver biopsy,” “NAFLD,” “NASH,” “sleeve gastrectomy,” “gastric bypass,” “fatty liver,” and “steatohepatitis.” The following exclusion criteria were initially applied: publication of abstracts only, case reports, letters, comments, languages other than English, and animal or in vitro studies. Studies were also excluded if there was no description of the bariatric surgery technique, had a follow-up of fewer than 6 months or longer than 24 months, and used a bariatric surgery technique other than RYGB (either open or laparoscopic) or LSG. After this initial screening, a full-text copy of each article was obtained for review. References within the selected articles were checked manually for additional relevant articles. Finally, we included only studies with baseline and follow-up paired biopsies, reporting NAS and/or fibrosis stage [13], in which the actual number or percentage of patients with each individual NAS feature grade (or at least mean NAS value) or fibrosis could be extracted. The selected studies were searched to extract data related to the research design, population, treatment, and outcomes. If needed, the original authors were contacted to provide for additional data and referenced as personal communication.

The data collected were recorded in a database (Microsoft Excel). Information extracted from eligible studies included basic study data (year, country, design, study size), and demographic data. Outcomes searched were individual grades of NAS features and fibrosis stage (steatosis 0, 1, 2, and 3; lobular inflammation 0, 1, 2, and 3; ballooning 0, 1, and 2; and fibrosis 0, 1, 2, 3, and 4), percentage of patients with NASH, NASH resolution rate, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, presented as U/L and body mass index (BMI) presented as kg/m^2. Two definitions for NASH were accepted: steatosis with inflammation and hepatocellular ballooning, or NAS

≥5. If NASH rates were not reported, NASH rates were calculated as the percentage of patients with NAS ≥5. NASH resolution rates were calculated as [(baseline NASH n – follow-up NASH n)/baseline NASH n × 100]. For all histological features, we recorded the number of biopsies evaluated at each time-point as the denominator. The overall rate of histological findings was estimated by using weighted averages of the sample prevalence in each study, with weights equal to the number of biopsies in studies reporting that outcome.

Definitions, natural history, clinical presentation, and standards for diagnosis and management of NAFLD

Definitions and natural history

The diagnosis of NAFLD is based on radiographic or histologic demonstration of ≥5% hepatic steatosis in the absence of other etiologies of liver dysfunction, including excessive alcohol consumption (more than 21 standard drinks each week for men and 14 per week for women), long-term use of steatogenic medications, genetic disorders, or other causes of secondary hepatic steatosis (Table 1) [5,14]. With a prevalence of 20% to 30% in Western studies, 44% to 64% of patient with NAFLD can progress to NASH over 3 to 7 years [15].

Histologically, the diagnosis of NASH requires hepatic steatosis of more than 5%, hepatocyte ballooning degeneration, and hepatic lobular inflammation with or without fibrosis [5]. Between 10% and 25% of patients with NASH may progress to advanced fibrosis and cirrhosis over 8 to 14 years, with progression of 1 fibrosis stage over an average of 7 years [16]. Overall, however, fibrosis progression in NAFLD has considerable variability among patients. Once cirrhosis (stage 4 fibrosis) develops, some studies note outcomes comparable to chronic hepatitis C–associated cirrhosis, while others show better outcomes with lower rates of liver-related complications and hepatocellular carcinoma [17–19].

Table 1
Common causes of secondary hepatic steatosis

Macrovesicular steatosis
Excessive alcohol consumption
Hepatitis C (genotype 3)
Wilson's disease
Lipodystrophy
Starvation
Parenteral nutrition
Abetalipoproteinemia
Medications (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids)
Microvesicular steatosis
Reye's syndrome
Medications (valproate, antiretroviral medicines)
Acute fatty liver of pregnancy
HELLP syndrome
Inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman's disease)

Adapted from Chalasani et al. [5].

Clinical presentation

The majority of patients with NAFLD and NASH are asymptomatic or have nonspecific symptoms such as fatigue or vague abdominal pain, with diagnoses of NAFLD made most commonly after workup for unrelated conditions. Among patients with steatosis, those at a higher risk of progression to NASH and subsequent fibrosis included, older patients, those with obesity, prediabetes, T2D, hypertension, hypertriglyceridemia, and/or metabolic syndrome [20]. Unfortunately, NASH is a silent disease and patients are often diagnosed in later stages once they have developed liver related complications. The American Association for the Study of Liver Diseases (AASLD) does not currently recommend screening high-risk patient populations including those with obesity and diabetes due to lack of available interventions with long-term benefits [14].This is in contrast with the recommendations from European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity, which recommend that patients with insulin resistance and/or metabolic risk factors (i.e., obesity or metabolic syndrome) should undergo workup for the diagnosis of NAFLD. Additionally, they recommend that individuals with steatosis be screened for secondary causes of NAFLD (Table 1), including a careful assessment of alcohol intake [21].

Serum biomarkers

Common first-line testing for patients with NAFLD and NASH include liver enzymes, with a focus on aminotransferases. ALT may be elevated in patients with NASH, however, with poor sensitivity, specificity, and no optimal cutoff value to diagnose NASH [22]. Regarding the AST/ALT ratio, NAFLD is generally ALT dominant, with a ratio typically less than 1, as opposed to alcoholic hepatitis which is AST dominant, with an AST/ALT ratio is usually over 2 [23]. This is important as there is significant variability in concordance of elevated liver enzymes and biopsy-proven NASH. Specifically, 11% to 30% of patients with biopsy-proven NASH have normal liver enzymes; if elevated, the degree to which aminotransferases are elevated does not correlate with the diagnosis of NASH, severity of fibrosis, or severity of inflammation. Unfortunately, an accurate assessment of the prevalence of transaminase elevation in the NASH population is difficult because many patients with NAFLD and NASH are diagnosed precisely because they are being worked up for abnormal liver enzymes. As such, apart from AST and ALT, there currently is no widely used or accepted laboratory testing for diagnosing NASH. Of note, cytokeratin-18 fragments and total cytokeratin-18, markers of hepatocyte apoptosis, have found some

clinical evidence to support workup of NASH but are not commercially available [24]. Patients being evaluated for bariatric surgery who are found to have elevations in liver enzymes should be evaluated for the presence and severity of liver disease.

Imaging

Currently, no imaging modalities can conclusively differentiate NAFLD from NASH and as such are limited to quantifying the degree of hepatic steatosis. Based on wide availability, patient tolerance, and low cost, conventional ultrasound is frequently the first test performed in patients with suspected NAFLD [25]. A large meta-analysis noted the sensitivity and specificity of ultrasound for diagnosing moderate-to-severe fatty liver, by virtue of the absence of steatosis, to be 85% (80%–89%) and 94% (87%–97%), respectively—slightly better than the overall accuracy of a noncontrast computed tomography scan [26]. However, conventional ultrasonography uses semiquantitative ordinal categories of liver fat (mild, moderate, and severe) with poor interobserver agreement [27]. It is also important to note that the sensitivity of ultrasound and computed tomography for detecting mild levels of steatosis is poor [26], and since liver fat decreases with the progression of fibrosis [28], these imaging methods might miss the population in greater need of identification and treatment.

Conversely, magnetic resonance imaging (MRI), measuring proton density fat fraction is the most accurate modality for the diagnosis of hepatic steatosis, with 92% to 100% sensitivity, 92% to 97% specificity, and the ability to reliably detect as little as 3% steatosis [29]. In patients with severe obesity, the common proton density fat fraction threshold for diagnosing steatosis is 5.4%, while 14.7% is the threshold for detecting moderate-to-severe steatosis [30]. However, MRI-associated costs and low patient tolerance limit its usefulness.

Individuals noted to have hepatic steatosis based on conventional ultrasound and suspicion of NASH based on serum biomarkers can be examined for advanced fibrosis and cirrhosis. Most commonly employed noninvasive methods include tests to assess liver stiffness as a surrogate of the degree of hepatic fibrosis. The underlying concept is that stiffer fibrotic tissue propagates waves faster than normal liver tissue. Liver stiffness can be measured by conventional ultrasound devices through acoustic resonance forced impulse imaging and shear wave elastography or be obtained through a dedicated device most commonly Vibration Controlled Transient Elastography (VCTE), which is commercially available as FibroScan or magnetic resonance elastography (MRE). Ultrasound transient elastography (FibroScan or VCT) is an FDA-approved device that uses the principles described in a device to measure the degree of both steatosis (measured in decibels per meter and ranging 100–400 dB/m) and stiffness (measured in kilopascals, ranging 2–75 kPa) with higher results suggesting higher steatosis and fibrosis respectively [31]. Studies have noted a sensitivity of 85% to 92% and specificity of 82% to 92% for diagnosing advanced fibrosis and cirrhosis in patients with NAFLD [32]. However, the thickness of the abdominal wall may limit its applicability in patients with severe obesity. Wan et al. [33] evaluated 83 bariatric surgery patients with VCTE using the XL probe and found a valid measurement in only 59% of the patients. However, when technically successful, there was a good reliability to diagnose severe steatosis and fibrosis, when compared to histologic examination. An additional advantage of Fibroscan is that it allows the examiner to simultaneously measure a variable called controlled attenuation parameter to assess liver fat. It is a rapid, point-of-care assessment with good sensitivity and specificity for the diagnosis of fatty liver [34]. Despite these strengths, specific limitations of controlled attenuation parameter include identifying the optimal cutoff value, implementing criteria for validity, and the impact of probe selection.

MRE, by comparison, has higher diagnostic accuracy compared to Fibroscan for each individual fibrosis stage and generally outperforms all ultrasound-based modalities with a lower risk of failure in patients with obesity [15,35,36]. A prospective study of MRE in patients with advanced fibrosis related to NAFLD, noted at a threshold of >3.63 kPa, sensitivity of 86% (95% confidence interval [CI]: 65%–97%), specificity of 91% (95% CI: 83%–96%), positive predictive value of 68% (95% CI: 48%–84%), and negative predictive value of 97% (95% CI: 91%–99%) in differentiating advanced fibrosis (stages 3 and 4) from early fibrosis (stages 0–2) [37]. However, MRE is relatively expensive, time-consuming to perform, and not widely available.

Noninvasive scoring systems

Few scoring systems are available to help in identifying patients at greater risk for NASH and/or advanced hepatic fibrosis. The NASH Clinical Scoring System [38] was constructed using demographic, clinical, and laboratory variables as predictors, specifically studying 200 consecutive subjects undergoing bariatric surgery without evidence of other liver disease. Six predictive factors for NASH were identified: the diagnosis of hypertension (score value 1), T2D (score value 1), sleep apnea (score value 1), AST >27 IU/L (score value 1), ALT >27 IU/L (score value 1), and nonblack race (score value 2). The scoring system can predict NASH with sufficient accuracy to be considered for clinical use, classifying the probability of NASH into 4 categories (low, intermediate, high, and very high). In the very high-risk group (summed points 6 to 7, 80% prevalence of NASH) a liver biopsy would very likely detect NASH, whereas in the low-risk group (summed points 0–2; 13% prevalence of NASH) a liver biopsy has a very low chance to detect NASH.

Considering noninvasive scoring systems designed to evaluate liver fibrosis, the NFS and the fibrosis 4 (FIB-4) index are commonly used scoring systems to stage the degree of fibrosis [39]. The NFS, which is specific to fatty liver disease, is calculated using age, BMI, hyperglycemia, AST/ALT ratio, albumin level, and platelet count and is readily available in an online calculator (https://nafldscore.com). A score of less than −1.455 has a 90% sensitivity and 64% specificity for stages F0 through F2 fibrosis (early fibrosis) and a score over 0.675 has a 60% sensitivity and 97% specificity for stages F3 and F4 fibrosis (advanced fibrosis). A score between −1.455 and 0.675 is considered indeterminate. The FIB-4 index, initially proposed to determine degree of hepatic fibrosis in patient with chronic hepatitis C infection [40], has also been validated in NASH and NAFLD. It uses age, ALT, AST, and platelet count to predict fibrosis and performs as well or better than the NFS for advanced fibrosis with patients in the indeterminate zone who require additional testing to evaluate fibrosis. About 30% of patients fall into the indeterminate zones for these tests and may need additional testing [39,41]. Both NFS and FIB-4 were better than other scoring systems [42].

Role of liver biopsy

Although there have been promising advancements in noninvasive testing, liver biopsy remains the gold standard assessment for identifying the presence of fibrosis and steatohepatitis in patients with NAFLD and is the only way to reliably distinguish NASH from NAFLD or other potential pathologies [5]. Table 2 summarizes the interpretation of histological findings according to the NASH Clinical Research Network [13], including NAS and NFS.

However, given that currently there are no approved NASH-specific therapies and lifestyle modification is recommended for all patients with NAFLD, the utility of liver biopsy is controversial. Should specific therapies become available, knowing if a patient has NASH and the extent of fibrosis may become more relevant to offer personalized approaches to care. Currently however AASLD recommends biopsy for only those patients with NAFLD who are at increased risk of steatohepatitis and/or advanced fibrosis and for patients in whom competing liver diseases, not NAFLD, are being considered or cannot be ruled out. In practice, in patients with NAFLD, liver biopsy is reserved for suspicion of advanced fibrosis where noninvasive testing shows discordant results [5,13,43].

In the context of MBS, it might be important to screen the patients for advanced fibrosis and cirrhosis, since it may prompt further preoperative evaluation and proper follow-up after surgery. Also, given the possibility of obtaining liver biopsies intraoperatively, bariatric patients might benefit from a tailored approach based on noninvasive scores and possibly added imaging. Udelsman et al. [44] demonstrated that, among 2465 undergoing bariatric surgery, a NFS <−1.455 ruled out advanced fibrosis (grades f3 and f4) in one-third of the patients, helping to guide further evaluations. Additionally, Chan et al. [45] retrospectively analyzed 759 patients with biopsy-proven NAFLD and tested the performance of a two-step approach screening for advanced fibrosis (grades f3 and f4), using NFS followed by transient elastography for patients with indeterminate (between −1.455 and 0.675) or high NFS (>0.675). In the subgroup with a prevalence of 3.7% of advanced fibrosis, with the 2-step approach only 25.6% of patients required transient elastography. A cutoff of 10 to 15 kPa (to rule out and diagnose advanced fibrosis, respectively) produced indeterminate or discordant results for 6.9% of patients and misclassified 2.7% of patients. In the subgroup with 10% of advanced fibrosis, transient elastography was required in 27.4% of patients. Thus, patients undergoing MBS might have the NFS calculated and be assessed for signs of portal hypertension and/or chronic liver disease, such as thrombocytopenia, esophageal varices, and ascites. In patients with indeterminate or high NFS and no signs of chronic liver disease, liver stiffness measure (through either ultrasound or MRE) or intraoperative liver biopsy should probably be considered, especially in those with higher risk of advanced fibrosis (older patients, T2D, hypertension, hypertriglyceridemia, and/or metabolic syndrome) [20]. Figure 1 shows a proposed algorithm for screening for advanced liver fibrosis in patients seeking MBS.

Table 2
Interpreting liver biopsy results for NAFLD

Histologic feature Result	Score NAFLD activity Score	 NAS[a] (0–8)
Steatosis (%)		
<5	0	
5–33	1	
34–66	2	
>66	3	
Hepatocyte ballooning degeneration		
None	0	
Few balloon cells	1	
Many balloon cells or prominent ballooning	2	
Lobular inflammation		
None	0	
<2 foci per 200× field	1	
2–4 foci per 200 × field	2	
>4 foci per 200 × field	3	
Fibrosis stage		
None		0
Perisinusoidal or periportal		1
Mild, zone 3, perisinusoidal		1a
Moderate, zone 3, perisinusoidal		1b
Portal/periportal		1c
Perisinusoidal and portal/periportal		2
Bridging fibrosis		3
Cirrhosis		4

Adapted from Kleiner et al. [13].
[a] NAS = steatosis + ballooning + lobular inflammation scores.

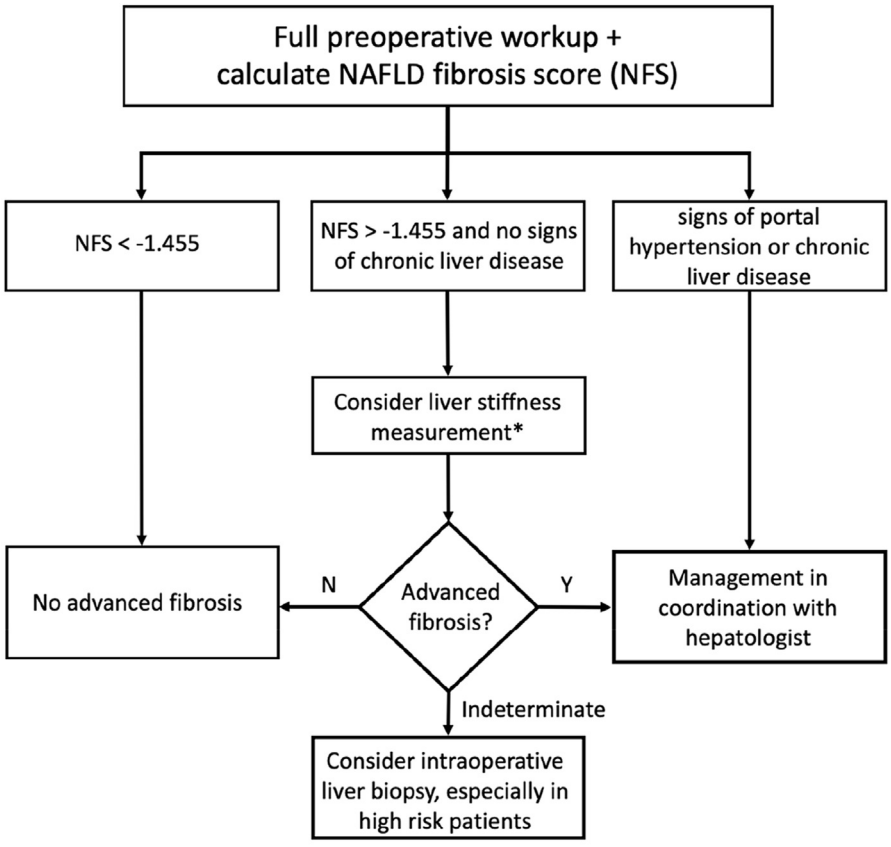

Fig. 1. Proposed algorithm for screening for advanced liver fibrosis in patients seeking bariatric surgery.

Some criteria should be followed for liver biopsy technique to maximize the assessment of NASH endpoints, either in the clinical setting or for clinical trials [14]: Needle core biopsies are preferred over wedge biopsies, using a needle $\leq$16 gauge; a tissue core $\geq$2 cm long (with the goal of providing $\geq$10 portal tracts for examination) represents the optimal biopsy length. These are also valid for biopsies taken during surgery.

Management of NAFLD and NASH

The primary treatment for NASH is lifestyle modification through diet and exercise, the ultimate goal being weight loss. The AASLD guidelines recommend that only biopsy-proven NASH and fibrosis should be considered for medical treatment [5]. Currently, the accepted endpoints for evaluating treatment modalities for NASH are the resolution of NASH without worsening fibrosis or the reduction of fibrosis stage without worsening NASH [11]. Although several drugs have been tested, there is yet no medical treatment approved for NASH.

A randomized placebo-controlled phase 3 clinical trial tested 10 mg or 25 mg daily of obeticholic acid (OCA), a farnesoid X receptor agonist, in NASH patients [46]. OCA failed to meet the NASH resolution endpoint (8% in the placebo group, 11% in the OCA 10 mg group [$P = 0.18$], and 12% in the OCA 25 mg group [$P = 0.13$]), but the fibrosis improvement endpoint was achieved by 12% patients in the placebo group, 18% in the OCA 10 mg group ($P = 0.045$), and 23% in the OCA 25 mg group ($P = 0.0002$). However, the FDA did not approve the drug because "the predicted benefit based on a surrogate histopathologic end point remains uncertain and does not sufficiently outweigh the potential risks" [47]. Recently, a randomized placebo-controlled Phase 2 clinical trial tested once-daily subcutaneous injection of 0.1, 0.2, or 0.4 mg of semaglutide, a glucagon-like peptide 1 agonist, in NASH patients with and without T2D [48]. The NASH resolution endpoint was achieved with no worsening of fibrosis in 40% in the 0.1-mg group, 36% in the 0.2-mg group, 59% 0.4-mg group, and 17% in the placebo group ($P < 0.001$ for Semaglutide 0.4 mg versus placebo). An improvement in fibrosis stage occurred in 43% of the patients in the 0.4-mg group and in 33% of the patients in the placebo group ($P = 0.48$). Malignant neoplasms were reported in 3 patients (1%) who

received semaglutide (1 with breast cancer in the 0.1-mg group; 1 each with endometrial adenocarcinoma and peripheral T-cell lymphoma in the 0.2-mg group) and in no patients who received placebo. Although in a recent meta-analysis including 55 921 patients, glucagon-like peptide 1 receptor agonists were not associated with an increased risk of malignant neoplasms [49], the safety profile of semaglutide as a treatment for NASH needs to be further investigated. An important confounding factor in the semaglutide trial is the medication-induced weight loss. Also, confounding the issue is the dramatic effect in the placebo arms of several clinical trials with around 15% of participants having resolution of NASH and improvement of fibrosis. Vitamin E supplementation has been recommended by AASLD in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this specific patient population. However, although 2 metanalyses have reported significant histological benefits with vitamin E in patients with NASH [50,51], its safety profile is not fully determined. According to the AASLD, risks and benefits should be discussed with each patient before starting therapy [5].

With the previously described drugs and several other drugs in the pipeline being developed and tested [52] but none yet approved, weight loss remains the primary treatment for NAFLD and NASH [11,53]. Only a few controlled studies presenting data from paired biopsies have been conducted evaluating lifestyle interventions and NASH endpoints. In a prospective study of 293 patients with NASH and mean BMI 31 kg/m^2 who underwent lifestyle modification for 12 months [54], mean body weight loss was 3.8%, NASH resolution was achieved in 25%, and fibrosis score improved in 19% but worsened in 16% after 12 months. Of note, incremental significant reductions in NAS were associated with weight loss. Among patients who lost >10% of their weight, 90% had resolution of NASH, and 45% had regression of fibrosis. However, only 10% of the patients achieved more than 10% weight loss. MBS is the only available treatment for patients with severe obesity that results in significant and sustained weight loss and improvement or remission of insulin resistance and T2D and also triggers metabolic mechanisms that improve liver histology independent of weight loss [55–59].

Review of the literature reporting the effect of RYGB and LSG on NAS features and fibrosis scores, in studies with paired liver biopsies

The literature was examined for studies with baseline and follow-up liver biopsies from patients undergoing bariatric surgery. Twelve studies fulfilled the inclusion criteria and were analyzed (Table 3). A total of 496 patients with paired liver biopsies are represented, with a mean age of 44.8 years, 65.5% female, 37.6% with T2D, 75.5% with hypertension, and mean BMI 46.8 kg/m^2 at baseline. The mean prevalence of NAFLD was 86.6%, and the mean prevalence of NASH

Table 3
Studies with baseline and follow-up paired liver biopsies reporting NAS and/or fibrosis in RYGB and LSG patients, with 6 to 24 months of follow-up

Study	Surgical technique	Paired biopsies (n)	Age (yr)	Female (%)	T2D (%)	HTN (%)	BMI Baseline	ALT Baseline	AST Baseline	NAFLD (%) Baseline	NASH (%) Baseline	Follow-up (mo))	BMI Follow-up	ALT Follow-up	AST Follow-up	NAFLD (%) Follow-up	NASH (%) Follow-up
Furuya et al. [62]	RYGB	18	46.6	94.4	44.4	72.2	51	28.2	25.4	100	61	24	31	21.8	25.1	11.1	0
Liu et al. [60]	LRYGB	39	41.4	84.6	–	–	47.7	34.5	30.8	–	58.9	18	29.5	23.7	25.6	–	0
Tai et al. [64]	LRYGB	21	29.9	61.9	28.6	52.4	43.8	34	27	90.5	19	12	28.3	24	27	4.8	0
Praveen Raj et al. [69]	RYGB (33.3%) LSG (66.7%)	30	44	50	50	40	45.9	37	31.3	96.7	6.7	6	35.3	25	22	36.7	0
Froylich et al. [70]	LRYGB (56%), LSG (44%)	25	51.8	64	48	84	60.6	39.7	–	–	–	18	43.1	–	–	–	–
Parker et al. [65]	LRYGB	15	46	70.7	–	–	48	31	29.9	87	86.7	16	–	20	23.6	27	13.3
Schwenger et al. [66]	LRYGB	42	47.2	76.2	34.2	–	48.1	29.3	28.4	85.7	21.4	12	34.5	23.6	23	19.1	2.4
Cabré et al. [67]	LSG	120	–	–	–	–	46.4	–	–	79.2	–	12	31.2	–	–	3.4	–
Leite et al. [61]	LRYGB	37	46.2	75.7	59.5	62.2	48.2	26.9	20.1	–	–	12	33.6	21.1	20.11	–	–
Chaim et al. [63]	Open RYGB	30	41	80	23.3	46.6	37.9	21	21	–	10.5	21	25.7	17	18	–	10
Salman et al. [68]	LSG	81	43.3	46	–	–	43.9	38	32	98.8	53.1	18	34.2	25	23	88.9	11.1
Allen et al. [71]	LRYGB (90%), LSG (10%)	38	50	86.8	–	–	44.6	–	–	68	10.5	12	32.4	–	–	5	0
	Total N, weighted averages (range)	496	44.8 (29.9–51.8)	65.5% (50–94.4)	37.6% (23.3–59.5)	75.5% (40–84)	46.7 (37.9–60.6)	32.4 (21–39.7)	28.4 (20.1–32)	86.6% (68–100)	36.7% (6.7–86.7)	14.5 (6–24)	32.5 (25.7–43.1)	22.9 (17–25)	22.8 (18–27)	28.5% (3.4–88.9)	2.8% (0–13.3)

RYGB = Roux-en-Y gastric bypass; LSG = laparoscopic sleeve gastrectomy

was 36.7%. Mean ALT and AST levels at baseline were 32.4 U/L and 28.4 U/L, respectively. After a mean follow-up period of 14.6 months, mean BMI, ALT, and AST were 32.5 kg/m^2, 22.9 U/L, and 22.8 U/L, respectively.

Table 4 depicts weighted averages (range) for baseline and follow-up histological findings from all studies and stratified by RYGB and LSG cohorts separately. Seven studies focused exclusively on RYGB [60–66] (either open or laparoscopic), and 2 studies examined LSG [67,68]. Two studies had both LSG and RYGB patients [69,70] and reported overall and separate data for each cohort. One study had 90% LRYGB and 10% LSG [71] (personal communication with Dr Yin Meng August 13, 2020), and therefore results were analyzed as LRYGB.

Eight studies reported mean NAS values, which varied from 3.8 at baseline to 1.3 at follow-up. Eight studies reported steatosis grades, and the percentage of patients without steatosis (grade 0) increased from 13.4% at baseline to 71.5% at follow-up. The same 8 studies reported grades of lobular inflammation and ballooning. At baseline, 72% had any grade of inflammation (scores 1, 2, or 3), and 61.7% had any grade of ballooning (scores 1 or 2). At follow-up, 70.9% had no inflammation (grade 0), and 72.3% had no ballooning (grade 0). The percentage of patients with NASH was reported (or possible to calculate) in 9 studies and dropped from 36.7% at baseline to 4.6% at follow-up, with a mean NASH resolution rate of 87.4%. None of the selected studies reported progression to NASH after surgery. Of note, the definition of NASH varied among studies, and only those that defined NASH as steatosis with inflammation and hepatocellular ballooning or NAS $\geq$5 were included in the analysis. In 1 study [63], 3 patients without steatosis at baseline presented steatosis after a mean follow-up of 27 months (1 patient developed hyperglycemia after surgery, and another regained weight).

Ten studies reporting fibrosis scores, and weighted averages are presented in Table 4. The proportion of patients without fibrosis increased from 29.8% at baseline to 58.7% at follow-up. The percentage of patients with fibrosis stages 1, 2, and 3 varied from 35.1%, 22.7%, and 12.1%, respectively, at baseline to 32.2%, 7.1%, and 1.9%, respectively, at follow-up. The percentage of patients with stage 4 fibrosis dropped from 1.4% at baseline to 0.9% at follow-up. Progression of fibrosis after surgery was reported in only 1 study [70] in 3 out of 14 patients who underwent LRYGB. On the other hand, as shown in Table 4, there was a significant improvement in fibrosis score in a majority of the patients, including those with stage 4 fibrosis. The cases without improvement of fibrosis were usually associated with more advanced NASH with fibrosis.

Table 4
Baseline and follow-up histologic features from paired biopsies

	Overall (12 studies, n = 496)		RYGB (10 studies, n = 264)		LSG (4 studies, n = 232)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Follow-up period	14.5 (6–24)		15.2 (6–24)		13.7 (6–18)	
Steatosis						
0	13.4% (0–32)	71.5% (11.1–96.6)	15.4% (0–32)	84% (40–95)	12.2% (1.2–20.8)	63.3% (11.1–96.6)
1	38.8% (22.2–61)	21.1% (3.3–60.5)	49.9% (38.1–61)	14.5% (4.8–50)	31.6% (22.2–38.3)	25.3% (3.3–60–5)
2	32% (10.5–46.7)	6.6% (0–24.7)	26.3% (10.5–60)	1.4% (0–10)	35.7% (30.8–42)	10% (0–24.7)
3	15.6% (0–34.6)	0.8% (0–3.7)	8.3% (0–16.7)	0%	20.4% (10–34.6)	1.4% (0–3.7)
Lobular inflammation						
0	28% (0–53.3)	70.9% (45.7–93.3)	36.2% (0–53)	72.9% (16.7–90.5)	20.4% (13.6–45)	69.7% (45.7–95)
1	37.3% (28.6–61.9)	27.9% (6.7–52.9)	41.7% (28.6–61.9)	25% (7.1–77.8)	34.4% (31.6–50)	29.8% (5–52.9)
2	24.6% (2–38.9)	1.1% (0–6.7)	18.6% (2–50)	2.1% (0–6.7)	30.8% (5–34.2)	0.4% (0–1.2)
3	10.1% (0–22.2)	0.3% (0–1.2)	3.5% (0–22.2)	0%	14.5% (0–19.8)	0.4% (0–1.2)
Ballooning						
0	38.3% (4.9–78.6)	72.3% (30.9–100)	46.5% (0–78.6)	84% (50–100)	29.4% (4.9–60)	64.7% (30.9–100)
1	40% (16.7–67)	24.9% (0–60.5)	32.1% (16.7–80)	16% (0–50)	47.9% (40–54.1)	30.8% (0–60.5)
2	23.2% (0–76.2)	2.7% (0–7.3)	25.6% (5–76.2)	0%	22.6% (0–54.3)	4.5% (0–8.6)
Fibrosis						
0	29.8% (0–87)	58.7% (23.3–94.6)	41.7% (0–87)	69.5% (23.3–95)	18.5% (12.3–55)	48.4% (40.7-95)
1	35.1% (3–57.1)	32.2% (0–57.1)	34.7% (3–57.1)	21.4% (0–57.1)	35.4% (15–42.8)	42.5% (0-50)
2	22.7% (0–33)	7.1% (0–23.3)	16.6% (0–30)	6.1% (0–23.3)	28.5% (10–32.5)	8.1% (0-16)
3	12.1% (0–30.9)	1.9% (0–7)	7.6% (0–21.4)	3.4% (0–10)	16.3% (7.5–30.9)	0.4% (0-1.2)
4	1.4% (0–5.6)	0.9% (0–6.7)	1.4% (0–10)	1.3% (0–6.7)	1.3% (0–10)	0.5% (0-5)
NAS	3.8 (2.1–6)	1.3 (0.2–3)	3.2 (1.8–4.9)	0.8 (0.2–1.97)	5.1 (2.6–6)	2.3 (0.4-3)
NASH	36.7% (6.7–86.7)	4.6% (0–13.3)	34.7% (0–86.7)	2.8% (0–13.3)	44.6% (10–53.1)	8.9% (0-11.1)
NASH resolution	87.4% (70–100)		91.9% (70–100)		80% (79.1–100)	

Data presented as weighted averages (range). Only biopsy proven NAFLD and NASH were analyzed.

T2D = type 2 diabetes; HTN = hypertension; BMI = body mass index; ALT = alanine transaminase; AST = Aspartate aminotransferase; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis

Histological features in RYGB and LSG cohorts

Table 4 summarizes the histologic features from RYGB and LSG cohorts separately. There were 264 RYGB patients with paired liver biopsies, from 10 studies [60–66,69–71], with a mean follow-up of 15.2 months, and 232 LSG patients with paired liver biopsies, from 4 studies [67–70], with a mean follow-up of 13.7 months. Mean NAS dropped from 3.2 to 0.8 after RYGB and from 5.1 to 2.3 after LSG. NASH rates dropped from 34.7% to 2.8% after RYGB and from 44.6% to 8.9% after LSG, with a mean NASH resolution rate of 91.9% after RYGB and 80% after LSG. It is important to observe that only 2 studies reported NASH rates in LSG patients, with the larger study demonstrating 53% of patients with NASH and a mean NAS of 6 at baseline.

The percentage of patients without fibrosis increased from 41.7% to 69.5% after RYGB and from 18.5% to 48.4% after LSG. In RYGB patients, the percentage of patients with fibrosis stages 1, 2, and 3 varied from 34.7%, 16.6%, and 7.6%, respectively, at baseline to 21.4%, 6.1%, and 3.4%, respectively, at follow-up. In LSG patients, the percentage of patients with fibrosis stages 1, 2, and 3 varied from 35.4%, 28.5%, and 16.3%, respectively, at baseline to 42.5%, 8.1%, and 0.4%, respectively, at follow-up. The proportion of patients with stage 4 fibrosis remained stable after RYGB (1.4%–1.3%) and decreased after LSG from 1.3% to 0.5%.

Our review of the literature did not allow for comparisons between LRYGB and LSG, since the populations in the studies were not comparable. However, in the studies presented here, both techniques resulted in significant improvement in biopsy proven NAFLD and NASH, with or without fibrosis. Additionally, RYGB and LSG provided for resolution or significant improvement in fibrosis, with rare cases of fibrosis progression after surgery.

Studies with miscellaneous or long-term outcomes

Unfortunately, very little data exist analyzing long-term paired liver biopsies. Only 2 studies reported 5-year outcomes after MBS. Lassailly et al. [72] reported 5-year outcomes for 64 patients with NASH (mean BMI = 48 kg/m^2) who underwent LRYGB and laparoscopic adjustable gastric band. The resolution of NASH with no worsening of fibrosis occurred in 84.4% of patients after 5 years. A subgroup analysis showed that 90.2% of LRYGB patients resolved NASH without fibrosis worsening, a significantly greater proportion than with laparoscopic adjustable gastric band (68.4%, $P = 0.03$). A decrease in fibrosis was documented in 70.2% of patients and resolution in 56% of all patients, with 45.5% resolution in patients with baseline bridging fibrosis. Schneck et al. [73] followed 9 female patients with NASH who underwent LRYGB. After 5 years NASH resolution was achieved in all 9 patients (100%). Fibrosis resolved in all 8 patients who had any degree of fibrosis at baseline (100%). One patient without fibrosis at the time of surgery had stage 1a fibrosis at follow-up.

Large studies reporting on paired liver biopsies over the long term are unlikely to become available due to the complexities of carrying out such studies. However, multiple studies have attempted to assess the long-term impact of MBS on NASH endpoints using noninvasive assessments. Klebanoff et al. [74] used the paired biopsy data from the long-term study by Mathurin et al. [75] to create a state-transition model and compare 3 different strategies for treating NASH: no treatment, intensive lifestyle intervention, and RYGB. Each intervention was tested in 16 patient profiles: 4 weight classes (overweight, mild obesity, moderate obesity, and severe obesity) and 4 stages of NASH disease (F0–F3). Outcomes included the gain in life-years, quality-adjusted life-years (QALYs), total costs, number of patients needed to treat (NNT) to prevent cirrhosis, liver-related death, and liver transplantation. The model showed that both surgery and intensive lifestyle intervention in patients with obesity (with F0–F3) increased QALYs by 0.678 to 2.152 and 0.452 to 0.618, respectively, compared with no treatment. Incremental cost-effectiveness ratios for surgery in all F0 to F3 patients with mild, moderate, or severe obesity were $48,836/QALY, $24,949/QALY, and $19,222/QALY, respectively. For bariatric surgery, the NNT values to prevent liver-related death in overweight F3 patients was 8; for patients with severe obesity and F3 the NNT was 11. The NNTs to prevent new cases of cirrhosis was 6 for patients overweight with F3 and 8 for patients with severe obesity and F3.

Recently, Wirth et al. [76] retrospectively assessed the possible impact of MBS on the progression to cirrhosis. A large insurance database was used to match 2942 NAFLD patients who underwent MBS and 5884 NAFLD patients who did not undergo surgery to evaluate differences in progression from NAFLD to cirrhosis. Median follow-up was approximately 32 months. During that time, 116 patients progressed to cirrhosis: 101 (1.7%) in the nonsurgical population and 15 (0.5%) in the bariatric surgery cohort. Hazards modeling found that bariatric surgery was independently associated with a decreased risk of developing cirrhosis (hazard ratio [HR]: 0.31, 95% CI: 0.19–0.52).

Lastly, Rustgi et al. [77] conducted a retrospective cohort study including 98,090 adult patients with severe obesity and newly diagnosed NAFLD, from a large nationwide database. The association between previous MBS and the risks of any cancer and obesity-related cancer was determined. A total of 33 435 patients (34.1%) received bariatric surgery. The adjusted risk of any cancer and obesity-related cancers was reduced by 18% (HR: 0.82; 95% CI 0.76–0.89) and 25% (HR: 0.65; 95% CI: 0.56–0.75), respectively, in patients with versus without MBS. In cancer-specific models, MBS was associated with a significant risk reduction for hepatocellular carcinoma (HR: 0.48; 95% CI: 0.24–0.89) in patients with NAFLD and severe obesity.

Conclusions

Our review of 12 studies, including 496 patients who were otherwise considered candidates for bariatric surgery, showed a mean prevalence of NAFLD of 86.6% and a mean prevalence of NASH of 36.7%. In that same population of patients with paired liver biopsies who underwent either LRYGB or LSG, the average NASH resolution rate was 87.4% (LRYGB: 91.9%, LSG: 80%) in a mean follow-up period of 14.5 months. Additionally, both surgical techniques resulted in significant improvement or resolution of liver fibrosis, with only rare cases of worsening fibrosis. These data suggest that at the very least LSG and RYGB do not worsen the progression of the disease. However, considering the absence of control groups in surgical studies with RYGB and LSG, the considerable effects of placebo on NASH and fibrosis changes in clinical trials (around 15%), and the paucity of comparative safety data, MBS in this patient population is not yet considered front-line therapy. Randomized controlled trials will be of paramount importance to determine the establish MBS as a formal treatment for NASH.

NAFLD is a major health issue in the United States and worldwide, inflicting a growing burden on patients' health and on the health system itself. Its association with obesity, insulin resistance and T2D makes it especially present in the daily practice of the bariatric surgeon. The recent consensus [4] proposing a change in the nomenclature to MAFLD reinforces the correlation between this disease and the bariatric population and should increase the awareness of the medical community about the disease. Importantly, the lack of approved medical treatment for NASH and the fact that lifestyle intervention fails to result in significant and sustained weight loss in patients with severe obesity make MBS a promising tool for management of patients with severe obesity and NASH.

Recommendations

I. Based on the evidence presented herein, MBS has a positive impact on NAFLD and NASH, either with or without fibrosis, and should be considered as a therapeutic tool among those patients with severe obesity. Randomized controlled trials are needed to determine whether MBS should be considered as a frontline therapy for NAFLD and NASH.

II. Considering that advanced hepatic fibrosis and cirrhosis might impact perioperative management and follow-up, patients referred for MBS may be screened for advanced fibrosis as detailed next. A tailored approach to guide the need for liver biopsy is proposed (Fig. 1) using noninvasive clinical scores (NFS, FIB-4), liver stiffness measure (LSM), and search for signs of portal hypertension or chronic liver disease (CLD):
   a. In patients with no signs of CLD and altered or indeterminate fibrosis scores, LSM may be considered (either FibroScan or MRE). In these cases, intraoperative liver biopsy might be an alternative to LSM.
   b. Patients with no signs of CLD and indeterminate LSM should be considered for intraoperative liver biopsy, especially in the presence of high-risk factors for advanced fibrosis (older patients, T2D, hypertension, hypertriglyceridemia, and/or metabolic syndrome). This will allow for proper follow-up after surgery.
   c. Patients with signs of chronic liver disease or advanced fibrosis measured by LSM should be managed in close coordination with a hepatologist prior to MBS as well as on follow-up.

III. For either clinical practice or clinical studies, needle core liver biopsies are preferred over wedge biopsies, using a needle $\leq$16 gauge. A tissue core $\geq$2 cm long (with the goal of identifying $\geq$10 portal tracts) represents the optimal biopsy length. These are also valid for biopsies taken during surgery.

IV. In clinical studies, researchers are encouraged to report liver histology according to NAS and fibrosis scores (Table 2) and define the accepted endpoints for NASH: resolution of NASH without worsening fibrosis or the reduction of fibrosis stage without worsening NASH.

Disclosures

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