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Nonalcoholic Steatohepatitis
A Review

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IMPORTANCE Nonalcoholic steatohepatitis (NASH) is the inflammatory subtype of nonalcoholic fatty liver disease (NAFLD) and is associated with disease progression, development of cirrhosis, and need for liver transplant. Despite its importance, NASH is underrecognized in clinical practice.

OBSERVATIONS NASH affects an estimated 3% to 6% of the US population and the prevalence is increasing. NASH is strongly associated with obesity, dyslipidemia, type 2 diabetes, and metabolic syndrome. Although a number of noninvasive tests and scoring systems exist to characterize NAFLD and NASH, liver biopsy is the only accepted method for diagnosis of NASH. Currently, no NASH-specific therapies are approved by the US Food and Drug Administration. Lifestyle modification is the mainstay of treatment, including dietary changes and exercise, with the primary goal being weight loss. Substantial improvement in histologic outcomes, including fibrosis, is directly correlated with increasing weight loss. In some cases, bariatric surgery may be indicated to achieve and maintain the necessary degree of weight loss required for therapeutic effect. An estimated 20% of patients with NASH will develop cirrhosis, and NASH is predicted to become the leading indication for liver transplants in the US. The mortality rate among patients with NASH is substantially higher than the general population or patients without this inflammatory subtype of NAFLD, with annual all-cause mortality rate of 25.56 per 1000 person-years and a liver-specific mortality rate of 11.77 per 1000 person-years.

CONCLUSIONS AND RELEVANCE Nonalcoholic steatohepatitis affects 3% to 6% of the US population, is more prevalent in patients with metabolic disease and obesity, progresses to cirrhosis in approximately 20% of cases, and is associated with increased rates of liver-specific and overall mortality. Early identification and targeted treatment of patients with nonalcoholic steatohepatitis are needed to improve patient outcomes, including directing patients toward intensive lifestyle modification to promote weight loss and referral for bariatric surgery as indicated for management of obesity and metabolic disease.

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Audio and Supplemental content

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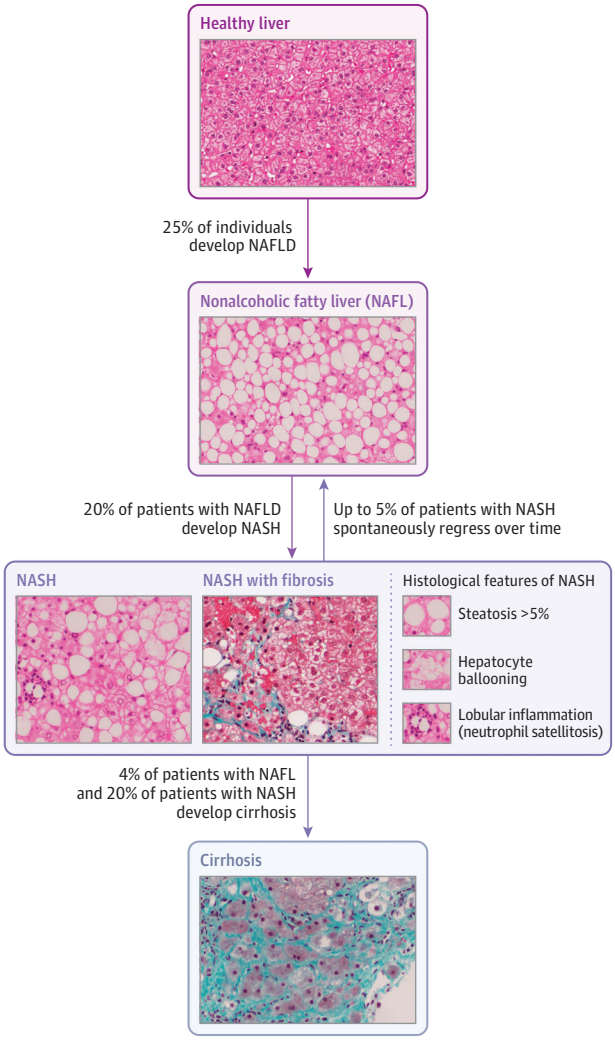
Nonalcoholic fatty liver disease (NAFLD) is one of the most commonly encountered liver disorders worldwide.[1] NAFLD is the spectrum of liver disease in which hepatic steatosis, the macrovesicular accumulation of triglyceride in hepatocytes, develops in the absence of secondary causes (eg, medications, excessive alcohol consumption, or certain heritable conditions).[2] Nonalcoholic steatohepatitis (NASH) is the inflammatory subtype of NAFLD, with steatosis as well as evidence of hepatocyte injury (ballooning) and inflammation, with or without fibrosis.[2] Although often clinically silent, with time NASH can progress to cirrhosis, end-stage liver disease, or the need for a liver transplant (**Figure 1**).

Although simple steatosis has a lower rate of progression—only about 4% of patients develop cirrhosis—more than 20% of patients with NASH will develop cirrhosis in their lifetime.[3] From 2004 to 2016, there was a 114% and 80% expansion in liver transplant waitlist registration due to NASH for men and women, respectively.[4] Due to this increase, NASH is now the leading indication for liver transplant listing for women and is expected to overtake alcoholic liver disease as the leading liver transplant indication for all patients within the next few years.[4] Patients with NASH have increased risk of hepatocellular carcinoma.[5] Lifetime direct medical costs for US patients with NASH in 2017 were estimated at $222 billion.[6] This estimate does not include indirect medical or societal costs and will only increase as the prevalence of NASH rises. NASH can be a diagnostic and therapeutic challenge for clinicians. This review will describe the epidemiology of NASH, its sequelae, and current approaches for diagnosis and treatment and will discuss diagnostic tools and therapies on the horizon.

Figure 1. Histologic Features and Epidemiology of Nonalcoholic Steatohepatitis



Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver disease including simple hepatic steatosis (NAFL) and nonalcoholic steatosis (NASH) with or without fibrosis or cirrhosis. When more than 5% hepatic steatosis is present, patients are considered to have NAFL. If steatosis is present along with hepatocyte ballooning degeneration and lobular inflammation, patients are considered to have NAFL. About 20% of patients with NAFLD have NASH. Over time, NAFL and NASH may progress to cirrhosis, with a greater proportion of patients with NASH (20%) developing cirrhosis in their lifetime.

Methods

A literature review was performed using PubMed to identify relevant English-language articles published through February 1, 2020. Search terms included *nonalcoholic steatohepatitis* in combination with *histology*, *epidemiology*, *diagnosis*, *cirrhosis*, *mortality*, *treatment*, *risk factors*, *liver transplantation*, *hepatocellular carcinoma* or *cancer*, *bariatric surgery*, and *fibrosis*. Additional relevant articles were identified from citations referenced in other articles, if they did not appear in the original search.

Epidemiology of NAFLD and NASH

A recent meta-analysis estimated the worldwide prevalence of NAFLD at about 25% (Figure 1).[7] There is significant geographic variability, with highest rates in the Middle East and South America (>30%) and lowest rates in Africa (13%). Previous population studies estimated that in the 2010s, 20% to 30% of the US population met criteria for NAFLD.[6,7] Prevalence appears to be increasing, with an estimated 3.6 million new cases annually.[8] Both NAFLD and NASH are more prevalent among males.[9] Racial and ethnic variations exist in NAFLD and NASH; in the US, NAFLD prevalence is highest among Hispanic and lowest among black populations.[9]

Directly estimating NASH prevalence at the population level is problematic because diagnosis requires a liver biopsy, which is infrequently performed. Biopsy case series of clinic outpatients or living donors for liver transplants found NASH in 1.4% to 15% of patients.[10-12] Overall population prevalence estimates may be indirectly extrapolated from liver biopsy case series and from voluntary or referred biopsies in studies involving patients with NAFLD. Using these methods, about 20% of all patients with NAFLD are expected to demonstrate NASH histology.[6-8] At the population level, most of these indirect estimates suggest that 3% to 6% of adults have NASH.[8] Based on current trends, the proportion of NAFLD patients with NASH is expected to increase over the next decade. According to 1 modeling study, the NAFLD population is projected to increase by 18% by 2030. The NASH population is projected to increase by 56%, to a total of 27 million individuals in the US.[13]

Both diseases are strongly associated with obesity, dyslipidemia, type 2 diabetes, and metabolic syndrome (**Table 1**). Patients with NASH are more likely to be obese or exhibit metabolic derangements than patients with only NAFLD or the general population, and the prevalence of NAFLD in patients undergoing bariatric surgery exceeds 90%.[19]

NASH and liver-specific disease outcomes are strongly associated with degree of hepatic fibrosis.[20] The severity of fibrosis, not the diagnosis of NASH, is predictive of long-term outcomes including overall mortality in patients with NAFLD.[21,22] A significantly higher proportion of patients with NASH have evidence of fibrosis on biopsy than patients with uncomplicated NAFLD.[21] Paired-biopsy (before and after treatment) studies have indicated that NASH may regress to NAFLD over time; patients who do not have NASH but whose biopsy result indicates fibrosis may represent patients in whom NASH was previously present but has regressed.[20] This meaningfully inflates the inherent placebo effect in clinical trials, making demonstration of therapeutic benefit more difficult. About 25% of patients' fibrosis is staged at F2 or greater at the time of NAFLD diagnosis (**Table 2**).[21] Around 40% of NASH patients have progression of their fibrosis over time, at a rate of about 1 stage per decade.[7] In 1 case series, at 15 years of follow-up, 11% of patients with NASH developed cirrhosis vs less than 1% of those with NAFLD.[24]

Patients with NASH develop hepatocellular carcinoma at significantly higher rates than the general population and have an annual rate that is 12 times higher than patients with NAFLD (5.77 vs 0.44 events per 1000 person-years).[7] Although hepatocellular carcinoma typically develops in the background of cirrhosis, patients with noncirrhotic NASH are still at increased risk.[5]

Table 1. Comorbid Conditions Associated With Nonalcoholic Steatohepatitis

Condition	% Estimated prevalence		
	General US population	Patients with NAFLD	Patients with NASH
Hypertriglyceridemia[7,14]	25.1	40.7	83.3
Obesity[7,15]	39.8	51.3	81.8
Dyslipidemia[7,16]	18.4	69.2	72.1
Metabolic syndrome[7,16]	34.3	42.5	70.7
Hypertension[7,17]	29.0	39.3	68.0
Type 2 diabetes[7,18]	14.0	22.5	43.6

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Table 2. Nonalcoholic Fatty Liver Disease Activity Score[a]

Histologic feature	Category	Score
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
Sum of steatosis, ballooning, and lobular inflammation scores		NAS score (0-8)
Fibrosis (F) grade		
	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

Abbreviations: NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

[a] By definition, patients must have a score of 1 or more in the categories of steatosis, hepatocyte ballooning degeneration, and lobular inflammation to have a diagnosis of NASH. A score of 5 or more is often associated with a diagnosis of NASH, but patients may have NASH with a score as low as 3. Fibrosis is scored separately from the NAS.[23]

Long-term studies have shown that compared with the general population, patients with NAFLD have higher overall and liver-specific mortality.[25] NASH has an annual mortality 1.7 times higher than NAFLD (25.56 vs 15.44 events per 1000 person-years), and liver-specific mortality is 15 times higher than in NAFLD (11.77 vs 0.77 events per 1000 person-years).[7] Despite increased liver-related mortality, cardiovascular disease is the primary cause of death for patients with both diagnoses, and increased risk of cardiovascular death appears to be the most significant factor related to the elevated risk of all-cause death for patients with NASH.[2,26]

Clinical Presentation

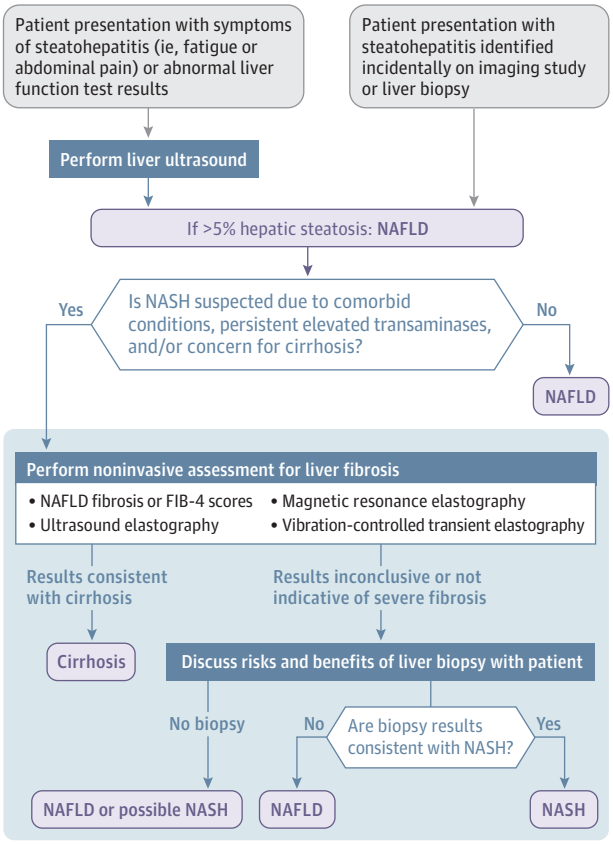
The majority of patients with NASH are asymptomatic or have nonspecific symptoms such as fatigue or vague abdominal pain. Most commonly, patients with NASH are identified after workup for unrelated conditions. A right upper quadrant ultrasound or computed tomographic (CT) scan that demonstrates steatosis or laboratory testing that shows elevated transaminases may prompt further workup for either NAFLD or NASH. If patients have not yet developed cirrhosis, the physical examination is typically unrevealing or demonstrates central obesity.

Liver ultrasound should be the first imaging study performed for patients with abnormal liver function test results and clinical concern about hepatic steatosis. Among patients identified as having steatosis, those who are obese or who have prediabetes or type 2 diabetes, hypertension, hypertriglyceridemia, or metabolic syndrome are at higher risk of NASH . Older patients are also more likely to have NASH than younger patients. However, patients may have NASH without any of these risk factors.

Defining and Diagnosing NASH

NASH was first described in 1980 and represents a state of chronic liver inflammation.[27] A NAFLD diagnosis requires either radiographic or histologic demonstration of more than 5% hepatic steatosis in the absence of excessive alcohol consumption. In contrast, a NASH diagnosis requires a biopsy with histologic examination

Figure 2. Diagnostic Approach to Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis



FIB-4 indicates fibrosis 4; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

demonstrating hepatic steatosis of more than 5%, hepatocyte ballooning degeneration, and hepatic lobular inflammation (Figure 1).[2] In response to varying definitions of NAFLD, a consensus statement on clinical trial design for NASH suggested an alcohol consumption threshold of less than 21 standard drinks each week for men and 14 drinks per week for women to characterize steatohepatitis as "nonalcoholic" (a "standard drink" being 1 oz [30 mL] of hard liquor, 4 oz [120 mL] of wine, or 12 oz [.36 L] of beer).[28]

Liver biopsy is currently the only accepted method to reliably differentiate NASH from simple steatosis, ie, uncomplicated NAFLD, although the need for and utility of liver biopsy in the setting of NAFLD is controversial.[2,29] This is because no NASH-specific therapies are currently approved, and lifestyle modifications are generally recommended for all patients with NAFLD, regardless of whether they have NAFLD or NASH.[30] Current society guidelines from the American Association for the Study of Liver Diseases (AASLD) recommend biopsy for patients with NAFLD who are at increased risk of steatohepatitis and/or advanced fibrosis and for patients in whom coexisting liver diseases cannot be ruled out.[2] High-risk patients include those with coexisting metabolic disease (Table 1), elevated aminotransferases, in particularly elevated alanine aminotransferase (ALT) relative to aspartate aminotransferase (AST), older age (>60 years), and Hispanic ethnicity. Noninvasive tests to predict fibrosis may help identify low-risk individuals and limit the number of patients who undergo biopsy. Liver biopsy is a near universal requirement for enrollment in clinical trials of NASH therapies and remains the most accepted method for monitoring treatment progress. Biopsy may also be helpful in providing prognostic information to patients. However, performing a liver biopsy on every patient with NAFLD is not feasible, cost-effective, or necessary.[30] A proposed diagnostic algorithm, which is based on clinical experience and AASLD guidelines, is presented in **Figure 2**.

Liver biopsy does have limitations. Although typically well tolerated, it can be painful and carry morbidity such as bleeding, infection, bile leak, damage to other organs, and rare mortality risk (<0.01%).[30] Biopsy adequacy, sampling error, and pathologist experience all affect diagnostic integrity, and concordance between pathologists is less than optimal for NASH-defining characteristics.[23,29] Discrepancies in pathologic interpretation have been noted in NASH clinical trials; 51 of the 247 patients (20.6%) enrolled in 1 trial based on an initial liver biopsy did not actually have hepatocellular ballooning (and therefore NASH) following central review of the enrollment biopsy specimen.[31]

Current guidelines recommend classifying biopsy specimens as "not NAFLD" (<5% steatosis), "NAFLD, not NASH," "borderline steatohepatitis" (when most but not all NASH criteria are met), and "definite steatohepatitis."[2] To provide a standard measure for histologic changes assessed in clinical trials for NAFLD, in 2005 the NASH Clinical Research Network (CRN) published the NAFLD activity score (Table 2). Fibrosis is the most important prognostic factor for the long-term outcomes of NASH but is not a requirement for its diagnosis. Most published NASH literature describes fibrosis based on criteria from the NASH CRN (Table 2) or a variation of the METAVIR (Meta-analysis of Histological Data in Viral Hepatitis) scoring system, which was originally developed to describe histology in hepatitis C.[20,32] However, several components of NASH fibrosis staging require better definition to improve clinical utility and reduce variation.[29] Improvement or worsening of disease activity may be associated with the regression or progression of fibrosis, respectively, in NAFLD.[33]

Noninvasive Evaluation of Suspected NASH

NAFLD is common and, when uncomplicated, typically asymptomatic, so hepatic steatosis is often incidentally diagnosed on imaging studies such as ultrasound or CT scan. Coexistent fibrosis and steatosis can make the ultrasound evaluation more difficult; 1 biopsy-controlled study involving patients with NASH showed that ultrasound missed 22% of steatosis diagnoses.[34] Steatosis may be detected on noncontrast CT, but due to similarity to or lower sensitivity than ultrasound, exposure to radiation, and potential for misdiagnosis, it is less useful than ultrasound as a screening test.[35] Magnetic resonance imaging is the most sensitive modality for the evaluation of hepatic steatosis (with 92%-100% sensitivity, 92%-97% specificity, and the ability to reliably detect as little as 3% steatosis) but is significantly more costly than ultrasound.[35] None of these imaging modalities can differentiate NAFLD from NASH, and they have limited ability to discern those patients with advanced fibrosis.

Noninvasive imaging–based evaluation for fibrosis primarily relies on measuring elastic shear wave propagation through liver parenchyma, with stiffer fibrotic tissue propagating waves faster.[36] The best-validated methods are transient elastography using ultrasound (eg, FibroScan) and magnetic resonance elastography (MRE).

FibroScan is a US Food and Drug (FDA)–approved bedside device with a sensitivity of 85% for detecting advanced fibrosis and 92% for detecting cirrhosis.[36] MRE has a sensitivity of 86% for identifying patients with advanced fibrosis.[37] Although individual studies have had conflicting results regarding the performance of ultrasound and MRE, a meta-analysis found that MRE had higher diagnostic accuracy for each individual fibrosis stage.[38] However, MRE is comparatively expensive, time-consuming to perform, and not widely available.[35]

Elevated ALT level is a commonly cited marker of progressive NAFLD or NASH. However, normal ALT levels do not preclude a diagnosis of NASH. The conventional ALT cutoff for enrollment in clinical trials or further testing is 1.5 times the upper limit of normal; however, at this cutoff, ALT has only 72% sensitivity and 51% specificity for the diagnosis of NASH.[39] When elevated, the AST:ALT ratio is typically less than 1.[40] However, studies indicate that 11% to 30% of patients with biopsy-proven NASH have normal ALT levels.[39,41,42] 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. The degree to which aminotransferases are elevated does not correlate with the diagnosis of NASH, severity of fibrosis, or severity of inflammation.[39,43] Elevated ALT levels have been associated with insulin resistance and degree of hepatic steatosis in patients with NASH, but again, patients with severe NASH may have normal liver enzymes.[41]

Other serum biomarkers have been explored to differentiate patients with NASH from those with NAFLD, but none is widely used or accepted for diagnosing NASH. Cytokeratin 18, a marker of hepatocyte apoptosis, is the only widely validated biomarker for NASH, but testing for it is not commercially available.[36] Numerous predictive models have used clinical and laboratory values to attempt to diagnose NASH, but because most were derived from morbidly obese populations, generalization to the overall NAFLD population is difficult, and these models have not been externally validated.

Noninvasive scoring systems may estimate a patient's degree of fibrosis without biopsy, with the most commonly used being the NAFLD fibrosis score and the fibrosis 4 (FIB-4) index .[35] The NAFLD fibrosis score, which is specific to fatty liver disease, is calculated from a formula using commonly available clinical parameters including patient age, body mass index, diagnosis of impaired fasting glucose or diabetes, AST:ALT ratio, albumin level, and platelet count.[44] The score may be useful for excluding advanced fibrosis, with a 90% sensitivity and 64% specificity for stages F0 through F2 fibrosis if the score is less than −1.455 and 60% sensitivity and 97% specificity for stages F3 and F4 fibrosis if the score is more than 0.675. However, many patients fall into the indeterminate zone between these cutoff values.[45]

The FIB-4 index, which predicts fibrosis based on age, ALT, AST, and platelet count, has been validated in NAFLD and NASH.[46,47] The index performed as well as or better than the NAFLD fibrosis score for advanced fibrosis.[35,47] However, the test relies on cutoff values to exclude or predict advanced fibrosis, and patients in the indeterminate zone require additional testing to evaluate fibrosis. Both the NAFLD fibrosis score and FIB-4 score perform as well as MRE in detecting advanced fibrosis and are available as online calculators.[2]

Treatment

Lifestyle Modification as NASH Therapy

NASH is a multifaceted condition with variable coexisting metabolic complications, making its treatment complex (Figure 2). The ideal therapy would effectively reverse the liver injury and fibrosis and improve or at least have no negative effects on other metabolic parameters or cardiovascular comorbidities. Although a wealth of information on the pathogenesis of NASH has accumulated during the past 10 years, no approved therapy for NASH is available. Currently, the primary treatment for NASH is lifestyle modification through diet and exercise, the ultimate goal being weight loss (**Table 3**).

Although dietary composition does appear to have an effect on hepatic fat deposition, no specific macronutrient diet has been shown to have a benefit for NASH. Therefore, caloric restriction is the most appropriate recommendation for these patients.[2] Fructose consumption should be limited because fructose has been associated with NASH development in patients with NAFLD and fibrosis progression.[48] Patients with NASH should also abstain from or significantly limit alcohol consumption, which is associated with hepatic injury and decreased chance of NASH resolution with treatment.[49]

Exercise decreases hepatic fat content independent of weight loss, reduces insulin resistance, and may modify de novo synthesis of free fatty acids, all of which may have an effect on NASH.[50] Although data are limited, vigorous exercise appears to limit the progression of NAFLD to NASH.[50]

Weight loss, regardless of how it is achieved, has the strongest association with histologic improvement in NASH. Weight loss of at least 5% appears necessary for improvement of hepatic steatosis among patients with NASH.[51] A meta-analysis of 8 studies showed that weight loss of 7% or greater was associated with improvement in the NAFLD activity score.[52] A prospective cohort study of paired liver biopsies in 261 patients found that all patients who lost more than 10% of their weight had reductions in their NAFLD activity score, and 90% had complete resolution of their NASH.[53] The study also suggested that weight loss of more than 10% may be associated with fibrosis regression, with this effect seen in 45% of patients. However, even more modest weight loss (≥5%) appeared to stabilize fibrosis.

Regardless of the method, 7% to 10% weight loss should be the first treatment goal for patients with NASH. However, less than 50% of patients are able to meet this goal through intensive lifestyle modification, even in well-monitored clinical trial settings.[52,53]

Bariatric Surgery and NASH

The degree of weight loss required for histologic improvement of NASH is difficult to achieve and harder to sustain. Bariatric surgery is the most effective weight-loss therapy and also improves comorbid diseases.[54,55] Risk of death from cardiovascular causes, the most common cause of death in NASH, is reduced after bariatric surgery.[52,56] Paired biopsy studies before and after bariatric surgery have shown substantial improvements in liver histology and NAFLD activity score, including decreased prevalence of NASH.[57,58] A prospective study involving 109 patients found that 85% no longer had NASH on biopsy 1 year after bariatric surgery, and 33% had fibrosis regression.[59]

Table 3. Treatment Approach for Nonalcoholic Steatohepatitis and Nonalcoholic Fatty Acid Liver Disease[a]

	NAFLD	Suspected NASH	Biopsy-proven NASH	NASH cirrhosis
Obtain baseline liver function tests including CBC, transaminases (AST/ALT), bilirubin, alkaline phosphatase, creatinine, INR	✓	✓	✓	✓
Medical optimization of comorbid conditions:				
Control of type 2 diabetes, hypertension, and dyslipidemia	✓	✓	✓	✓
Cardiovascular optimization				
Statin therapy as indicated by ACC/AHA guidelines				
Intensive lifestyle modification with goal of 7%-10% weight loss				
Caloric restriction	✓	✓	✓	✓
Aerobic exercise regimen				
Minimize alcohol use	✓	✓	✓	✓
Minimize added fructose intake	✓	✓	✓	✓
If patients are unable to achieve weight loss goal and may be otherwise eligible, refer for bariatric surgery evaluation	May consider, particularly for patients with BMI >35 or BMI >30 and type 2 diabetes	✓	✓	✓
Consider pioglitazone for patients with or without diabetes (30 mg/d)			✓	
For patients without diabetes, consider vitamin E (800 IU/d)			✓	
Consider eligibility for clinical trial participation		✓	✓	✓
Initiate screening for hepatocellular carcinoma per AASLD guidelines				✓
Initiate screening for esophageal varices per AASLD guidelines				✓
Consider evaluation for liver transplant if clinically decompensated				✓

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACC/AHA American College of Cardiology and American Heart Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CBC, complete blood cell count; INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

[a] Check marks indicate that the treatment strategy should be used.

Despite these improvements in NASH histology, bariatric surgery has historically been offered to patients with NASH only if they qualify through other obesity-related comorbidities. The 2018 AASLD guidelines state that "it is premature to consider foregut bariatric surgery as an established option to specifically treat NASH."[2] Most insurance approval of bariatric surgery relies on recommendations from the National Institutes of Health consensus conference on gastrointestinal surgery for severe obesity, which were published nearly 30 years ago; NASH is not considered a qualifying condition in this report.[60]

The safety of bariatric surgery for patients with NASH, and particularly patients with NASH cirrhosis, is not well established. Most studies of perioperative mortality include patients with cirrhosis diagnosed at the time of surgery, so these results are therefore difficult to generalize to elective bariatric surgery for the treatment of NASH.[61] Among patients with NASH requiring liver transplant, comorbidities including obesity persist after transplant. Bariatric surgery may have a role to play in preventing liver transplant for some patients or preventing NASH recurrence after transplant. Although small studies suggest coexistent bariatric surgery and liver transplant are possible, the optimal timing and procedure are not clear.[62]

Pharmacotherapy for NASH: Current Knowledge

Although no specific pharmaceuticals are currently FDA approved for NASH, vitamin E (an antioxidant) and pioglitazone (a thiazolidinedione insulin sensitizer acting through peroxisome proliferator–activated receptor [PPAR]-γ agonism) have shown some benefit in randomized trials. The phase 3 Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial randomized 247 patients with NASH but not diabetes to receive treatment with placebo, pioglitazone 30 mg, or vitamin E 800 IU for 96 weeks.[31] Compared with placebo, vitamin E therapy demonstrated improvement in the primary end point of an improvement in the NAFLD activity score by 2 or more points (at least 1 point in hepatocellular ballooning and 1 point in steatosis or lobular inflammation) and no increase in fibrosis (43% vs 19%, $P = .001$), whereas pioglitazone did not reach statistical significance (34% vs 19%, $P = .04$). Given the dual comparison with vitamin E and pioglitazone, a P value of .025 was considered significant in this study.

There were, however, discrepancies in the assessment of the presence of ballooning between the inclusion and central review pathology reports, and more patients with this initial misclassification were in the pioglitazone group. Meeting the primary end point was dependent on improvement in the hepatocellular ballooning score, so this disagreement in histologic assessments may account for the failure of pioglitazone to meet the end point. Neither vitamin E nor pioglitazone improved fibrosis over placebo. In the trial, only a subset of patients had a treatment response, and the effect of placebo treatment was considerable. Notably, 47% of patients treated with pioglitazone and 36% of patients treated with vitamin E had resolution of their steatohepatitis compared with 21% of patients treated with placebo alone. This secondary end point led the AASLD to conclude that pioglitazone or vitamin E may be used to treat patients with biopsy-proven NASH.[2] However, concerns about the safety of vitamin E supplementation in other diseases have been raised, with increased risk of hemorrhagic stroke and prostate cancer,

as well as conflicting reports of increased overall mortality.[63-66] Overall, the utility of vitamin E and pioglitazone for the treatment of NASH is uncertain.

A small phase 2 trial (involving 52 patients) that evaluated liraglutide, a synthetic long-acting glucagon-like peptide 1 (GLP-1) agonist currently available for treatment of type 2 diabetes and obesity, found the drug effective for patients with NASH in terms of weight loss, resolution of steatohepatitis, and less progression of fibrosis than placebo, although gastrointestinal adverse effects were seen, including diarrhea, constipation, and appetite loss.[67] Further study is needed before liraglutide can be recommended for NASH treatment.

Modification of cardiovascular risk factors is an important aspect of treatment.[2] Statin therapy is safe for patients with liver disease and should be prescribed for all high-risk patients based on guidelines.[68,69] Some evidence suggests that statins may independently treat NASH.[70] Pharmaceutical weight loss agents have not been extensively studied for NASH, but given the strong correlation between the degree of weight loss and improvement in liver histology, these drugs may benefit some patients as an adjunct to other therapies.

The Future of NASH-Specific Therapies

The complex pathophysiology underlying the development and progression of NASH and its interplay with other metabolic disease processes is wide reaching and incompletely understood. As a result, NASH therapeutics under current exploration have a broad range of targets: alterations in the microbiome and gut permeability, oxidative stress, insulin resistance, apoptosis, lipotoxicity, inflammation, bile acid metabolism, and fibrogenesis, among others. Currently, 6 compounds under investigation have had completed phase 2 clinical trials and moved to phase 3, with dozens of additional therapies in phase 2 trials (phase 3 trials are described in eTable 1 in the Supplement). No clinical trial to date has had more than 50% of patients meet a primary treatment end point. Given the multiple pathways implicated in NASH pathogenesis and observed response from single-agent therapies, combination and individualized regimens will likely be needed to adequately treat NASH.

Conclusions

Nonalcoholic steatohepatitis affects 3% to 6% of the US population, is more prevalent in patients with metabolic disease and obesity, progresses to cirrhosis in approximately 20% of cases, and is associated with increased rates of liver-specific and overall mortality. Early identification and targeted treatment of patients with nonalcoholic steatohepatitis are needed to improve patient outcomes, including directing patients toward intensive lifestyle modification to promote weight loss and referral for bariatric surgery as indicated for management of obesity and metabolic disease.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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