Clinical Roundtable Monograph

Noninvasive Tests (NITs) in the Management of Nonalcoholic Steatohepatitis (NASH)

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Abstract: Nonalcoholic fatty liver disease (NAFLD) affects approximately a quarter of the adult population in most Western countries, particularly those in Europe and North America. Patients may progress from isolated steatosis through nonalcoholic steatohepatitis (NASH) to fibrosis. Among patients with NASH, fibrosis predicts long-term outcomes, including liver-related sequelae, cardiovascular disease, and all-cause morbidity and mortality. The classic approach to assessing disease severity in this setting is with liver biopsy. The challenges associated with biopsy led to the development of noninvasive testing strategies in NASH. There are 2 broad categories of noninvasive tests: biochemical biomarkers (or so-called "wet biomarkers") and imaging biomarkers. Biochemical biomarker tests include the NAFLD fibrosis score (NFS), the FIB-4 score, and the aspartate transaminase to platelet ratio (APRI) test. There are also proprietary biochemical biomarkers. Imaging tests include vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE), and multiparametric magnetic resonance imaging, such as corrected T1 (cT1). These tests work best in excluding the presence of advanced disease. Accuracy and positive predictive value are improved when the tests are used in combination or sequentially, by decreasing the proportion of patients with indeterminate values. Current management strategies reflect the disease stage. Diet and lifestyle modifications are important across the spectrum of disease. Results from the recent phase 3 REGENERATE trial suggest that obeticholic acid may improve hepatic fibrosis in patients with NASH-associated fibrosis. The MAESTRO-NASH trial is comparing resmetirom, a thyroid hormone beta receptor agonist, vs placebo. The REVERSE study is evaluating obeticholic acid in patients with NASH and cirrhosis. Data from these and other trials will provide evidence regarding the utility of newer agents for the treatment of NASH and NASH-related fibrosis.

Staging of Fibrosis in Nonalcoholic Steatohepatitis (NASH): Implications for Prognosis

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Nonalcoholic fatty liver disease (NAFLD) is an extremely common condition, and its prevalence is predicted to increase.[1] Obesity, a primary driver of NAFLD, is increasing[2]; the majority of the modern general population weighs more than in previous generations. NAFLD affects approximately a quarter of the adult population in most Western countries, particularly those in Europe and North America.[3,4] The rate may be even higher in South America and the Middle East, although there are relatively few studies in these populations on which to base estimates.

It is known that fatty liver progresses to cirrhosis and/or hepatocellular carcinoma in a significant minority of cases.[5] Patients progress from steatosis (nonalcoholic fatty liver [NAFL]) to nonalcoholic steatohepatitis (NASH), which is the inflammatory form of the disease, and fibrosis. Histologically, fibrosis is categorized on a scale from F0, which is essentially no fibrosis, to F4, which indicates cirrhosis. Several studies have provided insight into the factors that drive progression. The more features of the metabolic syndrome an individual exhibits, the greater the risk of steatohepatitis and progressive fibrosis.[6] Increased severity of diabetes, obesity, hypertension, and dyslipidemia cor-

relate with more fat in the liver[7] and a higher likelihood of progression to steatohepatitis and fibrosis.

The natural history of fatty liver disease is dynamic, with disease severity "waxing and waning" under the influence of environmental factors that act on a polygenic background of varying susceptibility. This observation is

> Intervening in a timely manner could prevent subsequent progression to cirrhosis, and consequent worsening of symptom burden and morbidity.

supported by data from dual biopsy studies showing that the severity of fatty liver disease fluctuates.[8,9] These studies identified progression in approximately 40% of patients,
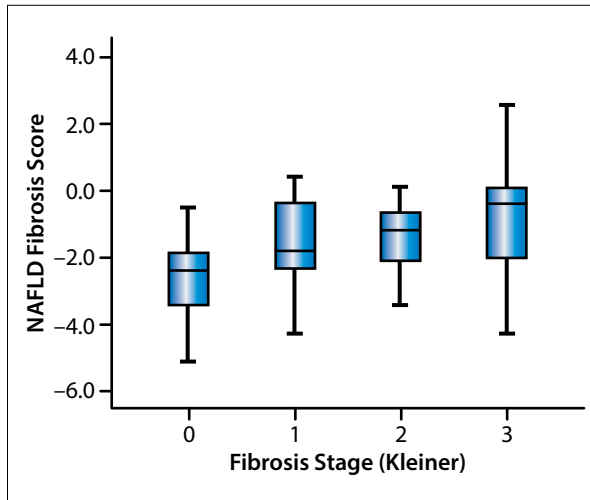
Figure 1. The relationship between the stage of fibrosis and the NAFLD fibrosis score. NAFLD, nonalcoholic fatty liver disease. Adapted from McPherson S et al. *J Hepatol.* 2015;62(5):1148-1155.[8]
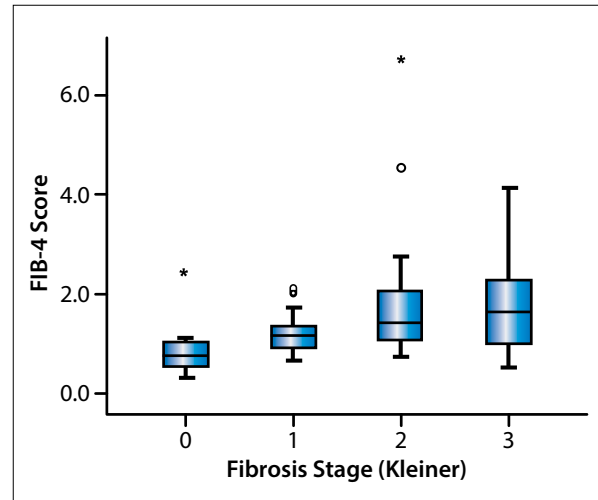

Figure 2. The relationship between the stage of fibrosis and the FIB-4 score. Adapted from McPherson S et al. *J Hepatol.* 2015;62(5):1148-1155.[8]

no change in 40%, and regression in 20%. The stage of fibrosis corresponds to the NAFLD score and the Fibrosis-4 (FIB-4) score (Figures 1 and 2).[8]

Steatohepatitis is an established driver of disease pathogenesis. However, an interesting observation from longitudinal studies is that the presence or severity of steatohepatitis does not correlate well with long-term outcome.[10] In contrast, fibrosis has consistently been identified as the condition that best predicts long-term outcomes, including liver-related sequelae, cardiovascular disease, and all-cause morbidity and mortality.[11] Some controversy therefore surrounds the prognostic value of steatohepatitis, although the reasons for this apparent discrepancy probably relate more to the limitations of liver biopsy as a diagnostic test (eg, sampling error, interobserver variation among pathologists), rather than a lack of relevance of steatohepatitis. In this respect, fibrosis is a more tractable phenomenon than steatohepatitis. It is therefore easier to measure fibrosis in longitudinal studies to demonstrate correlation with outcomes.

Symptoms

Traditionally, fatty liver had been considered asymptomatic, particularly so in patients who have not developed hepatic decompensation due to cirrhosis. Recent data, however, now suggest there is significant symptom burden with fatty liver disease. In precirrhotic fatty liver disease, the severity of symptoms may correlate with the degree of fibrosis or, more contentiously, possibly also with the activity of steatohepatitis.[12,13] Patients may experience a variety of largely nonspecific symptoms, including fatigue, nonspecific abdominal pain, and clouded thinking as the

liver disease progresses.

Patients with more fibrosis are more likely to experience adverse disease outcomes.[14] It therefore makes sense to identify patients with fibrosis, even at relatively early stages. Intervening in a timely manner could prevent subsequent progression to cirrhosis, and consequent worsening of symptom burden and morbidity. Early detection of fibrosis is beneficial for patients with fatty liver, and will remain an important underpinning feature of management.

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Use of Noninvasive Tests (NITs) in Patients With Nonalcoholic Steatohepatitis (NASH)

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The classic approach to assessing disease severity in NASH is with liver biopsy. Although biopsy has many disadvantages, it still has a role in this setting. Several key aspects of this procedure are helpful to guide therapeutic intervention and management. Biopsies enable visualization of the architecture of the liver. Information gained by examining cell types under a microscope can be combined with clinical data. It is possible to exclude coexistent diseases, such as autoimmune hepatitis, cholestatic injury, and drug-induced liver injury. It is important to rule out drug-induced liver injury because many of these patients are taking multiple medications, including herbs and supplements, in an attempt to improve their overall health. Paradoxically, in some cases, these medications can

have a negative impact on the liver. In a patient with NAFLD, mild elevations of liver enzymes may escape notice of the clinician.

The disadvantages to liver biopsy in this setting are straightforward. A common disease like NAFLD requires an evaluation tool that is more acceptable to patients, easier to obtain, and provides information that is as good, if not better, to guide clinical decisions. Biopsy is invasive. Associated risks include bleeding, pain, hospitalization, time away from work, and even death, in very rare cases.[1] There are also issues with inter- and intra-observer variability. NAFLD is heterogeneous. There are 8 segments in the liver, and each may have different levels of disease activity, fibrosis, and even fat. A liver biopsy provides approximately 1/50,000 of the liver for interpretation.[2]

A common analogy is a motion picture, which consists of numerous individual small frames each telling a part of the story. The entire story is not known until all of the frames are seen, and it can be challenging to extrapolate from one image.

These challenges underline the need for noninvasive testing in NASH, and most clinicians believe the field will evolve to encompass this strategy. The real challenge is that we are held to an imperfect gold standard. The incorporation of noninvasive testing raises questions regarding the different contexts of use as well as the various types. There are biochemical biomarkers and imaging biomarkers, which can be used alone or together. Clinicians can test individual markers or multiple markers. Sequential testing can also be used.

Noninvasive tests can be used in 3 different contexts. In the United States, there are approximately 80 to 100 million patients with fatty liver.[3] Approximately 20% to 25% of these patients have NASH with some degree of fibrosis. A test is needed to help identify these at-risk patients. The first context of use for noninvasive tests would be for the diagnosis and identification of NASH with fibrosis, as well as for the staging of fibrosis. Most clinicians agree that stage 2, 3, or 4 fibrosis defines a patient as high risk. The second context of use for noninvasive tests would be for treatment monitoring. There will likely be pharmaceutical treatments for NASH in the near future. Noninvasive testing could determine how well the drug is working, and help guide decisions regarding whether the drug should be stopped or continued, with or without dose modification. Research is ongoing to develop noninvasive tests for monitoring. A third area of use would be to assess long-term prognosis. It may be possible to perform a simple test that will predict a patient's risk for a negative outcome in 5 or 10 years.

Types of Noninvasive Tests

There are many noninvasive tests available. Noninvasive tests can be divided into 2 broad categories: biochemical biomarkers and imaging biomarkers. The following tests are those most often used in studies of NASH, and are most likely to be available to practicing clinicians.

Biochemical Biomarkers

The tests with the most supporting data are the FIB-4 and the NAFLD fibrosis score (NFS). These tests were developed more than a decade ago. The FIB-4 test consists of age, aspartate transaminase (AST), alanine transaminase (ALT), and platelet count.[4] The NFS includes age, body mass index, the presence or absence of diabetes, platelets, AST, ALT, and albumin.[5,6] Using the receiver operating characteristic (ROC) curves to predict death, researchers

> Accuracy is improved when the tests are used in combination or sequentially, by decreasing the proportion of patients with indeterminate values.

found that a baseline NFS of –0.9 was the best cutoff value, with a sensitivity of 62%, a specificity of 76%, a positive predictive value of 28%, a negative predictive value of 93%, and an area under the curve of 0.7 (Figure 3).[6] A sensitivity comparison of the NFS and the FIB-4 is shown in Figure 4.[4]

The FIB-4 score was originally developed for patients with hepatitis C and HIV coinfection to estimate the amount of fibrosis in the liver.[7] This score was subsequently applied to NAFLD. Online calculators are available to provide the FIB-4 score. These tests use a lower cutoff to optimize sensitivity and a higher cutoff to optimize specificity. There is a large indeterminate range. Both of the tests are best suited for their negative predictability—in other words, they can be used to exclude the presence of advanced fibrosis.
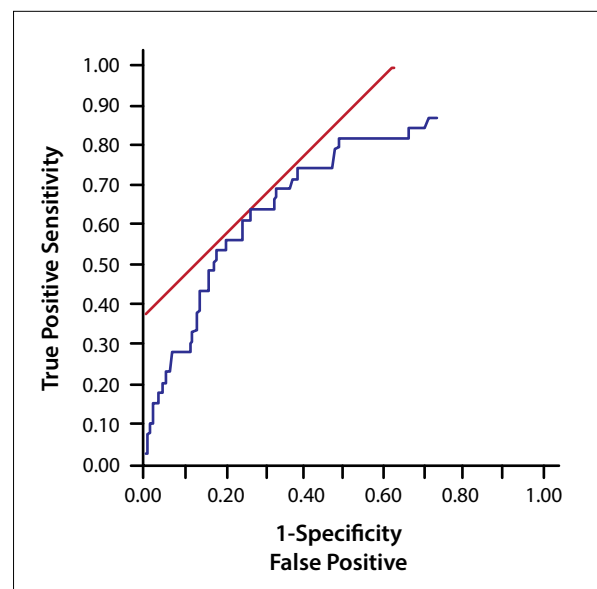

Figure 3. The baseline nonalcoholic fatty liver disease fibrosis score can predict death. Adapted from Treeprasertsuk S et al. *World J Gastroenterol.* 2013;19(8):1219-1229.[6]
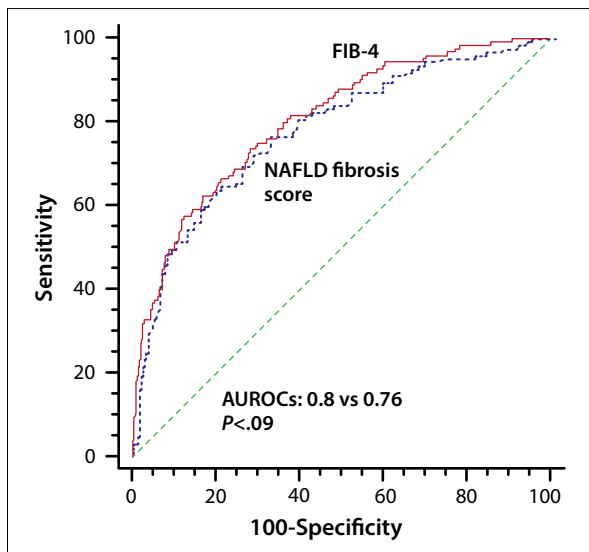
Figure 4. Sensitivity of the FIB-4 and NAFLD fibrosis score. AUROCs, area under receiver operating characteristic curves; NAFLD, nonalcoholic fatty liver disease. Adapted from Shah AG et al. *Clin Gastroenterol Hepatol.* 2009;7(10):1104-1112.[4]

The AST to platelet ratio (APRI) test evaluates AST and platelet count. This test divides the AST by the upper limit of normal, divides that sum by the platelet count, and multiplies that value by 100. Reports in the literature suggest that the APRI test can be predictive, particularly for cirrhosis and advanced liver disease.[8] In my experience, this test is not utilized much, and I do not find it to be that helpful.

There are also proprietary biochemical biomarkers. The FibroSure® test uses a proprietary algorithm to evaluate 6 different biomarkers.[9] Again, this test has not been optimized for its positive predictive value.

All of the biochemical tests work best in *excluding* the presence of advanced disease, which is helpful information. For up to a third of patients, results will fall between the low cutoff and the high cutoff, and thus will be indeterminate. These tests are also predicated on the prevalence of advanced disease in the cohort of patients tested. For example, noninvasive tests such as the FIB-4 and NFS are more predictive for advanced liver disease in a tertiary care referral center, where the underlying prevalence of advanced disease is higher.

There are 2 additional tests that measure extracellular matrix turnover, or fibrosis: the Enhanced Liver Fibrosis (ELF) test and PRO-C3. These tests are undergoing extensive study and are not yet readily available for clinical practice. The ELF test consists of hyaluronic acid, TIMP-1, and P3NP.[10,11] In clinical trials of simtuzumab and selonsertib, researchers evaluated the predictive capabilities of ELF.[12,13] A cutoff of 9.8 was predictive of cirrhosis. A cutoff of 11.3 was associated with a fivefold

higher risk of liver-related complications.

PRO-C3 is a biochemical, collagen biomarker that is associated with fibrogenesis, matrix turnover, and development of fibrosis.[14] The cutoff values associated with this test are unclear. Boyle and colleagues studied this test with a combination of clinical markers known as ABC3D.[15] (Within that acronym, C3 refers to PRO-C3.) At a cutoff of 14.5 ng/mL, PRO-C3 showed fair sensitivity and specificity for identifying NASH patients with some degree of fibrosis. The overall accuracy at this cutoff was approximately 64%. Use of a cutoff of 16.5 ng/mL for a cirrhotic cohort had a similar accuracy of approximately 68%.

The NIS4™ test combines 4 different biomarkers: miR-34a, alpha-2 macroglobulin, YKL-40, and hemoglobin A1c. This test was developed to identify at-risk NASH (NAS ≥4 and F ≥2). It is not yet ready for clinical practice, but it shows promise.[16]

Imaging Biomarkers

Several imaging biomarkers are commonly used in clinical trials and are being studied extensively in other scenarios. They include vibration-controlled transient elastography (VCTE; eg, FibroScan®), magnetic resonance elastography (MRE), and multiparametric magnetic resonance imaging (MRI), such as corrected T1 (cT1). MRE estimates the average extent of fibrosis throughout the liver.[17-20] MRE and cT1 are MRI-based imaging modalities, and therefore patient accessibility limits their use.

Transient elastography is now portable and used more frequently. Use of transient elastography is limited primarily by cost, and also by reimbursement issues. This method is gaining traction for its negative predictive value. It is a simple, noninvasive test that can be performed in approximately 10 minutes in the clinic. Transient elastography provides the clinician with 2 numbers. The controlled attenuation parameter (CAP) indicates the presence of fat in the liver. The CAP score is measured in decibels per meter (dB/m), and a cutoff of approximately 280 dB/m predicts fatty liver. Transient elastography also measures liver stiffness correlating to fibrosis.[17] Stiffness is measured in kilopascals (kPa). Values of less than 6 kPa indicate a low likelihood of fibrosis. This test can be administered to patients during clinic visits to assess the presence and extent of fatty liver.

Many clinicians use FibroScan® to identify a patient's stage of disease. I would caution against this use. Although this tool is very helpful in clinical practice, it is not accurate enough to reliably distinguish different stages of disease severity when used alone. In my practice, an abnormal FibroScan® result—a value greater than approximately 8.5—indicates a risk for fibrosis in the setting of fatty liver that warrants further workup.

Diagnosis of NASH With Fibrosis

For the diagnosis and identification of NASH with fibrosis, these tests are best utilized for their negative predictive value. However, it is possible to optimize sensitivity, and begin to consider positive predictive value, when these tests are used together. Accuracy is improved when the tests are used in combination or sequentially, by decreasing the proportion of patients with indeterminate values.

A combination strategy known as the FAST score consists of FibroScan® plus AST.[21] This score is calculated by an app based on 3 values: the AST; the CAP from FibroScan®, which indicates the amount of fat; and the kPa value. The FAST score provides an upper and lower cutoff, but with a smaller indeterminate range. The ROC curve for the FAST score is shown in Figure 5.

An example of sequential testing would be to administer the FIB-4, followed by the ABC3D score. This strategy would improve accuracy beyond that of each single test alone.[15] The field may be moving in the direction of using a simple test followed by another blood test. Another way would be to combine a wet biomarker with an imaging biomarker. Research is evaluating these approaches.

Treatment Monitoring

Two tests—one imaging test and one wet biomarker test—have come to the forefront for predicting response to therapy. The proton density fat fraction has become the gold standard for measuring fat in the liver.[22] The degree to which the fat fraction drops with therapeutic intervention has been correlated with resolution of underlying steatohepatitis,[23-25] and even improvement of fibrosis.

Measurement of ALT is a routine biochemical test for liver disease. A certain magnitude of effect drop in ALT is linked to improvement in the components of steatohepatitis and fibrosis. The current cutoff value is approximately 17 units/L.[26]

The best use of these tests is still being honed. They will most likely not be used with every therapeutic modality, and drugs with different mechanisms of action may have different effects on biomarkers. Other strategies are in development.

Prognosis

Recent studies have evaluated the use of 2 different biomarkers to predict prognosis: the ELF test and multiparametric MRI with the cT1 platform. With the ELF test, values higher than 9.8 were linked to progression to cirrhosis.[27] Values higher than 11.3 were associated with a higher risk for liver-related complications. Some data
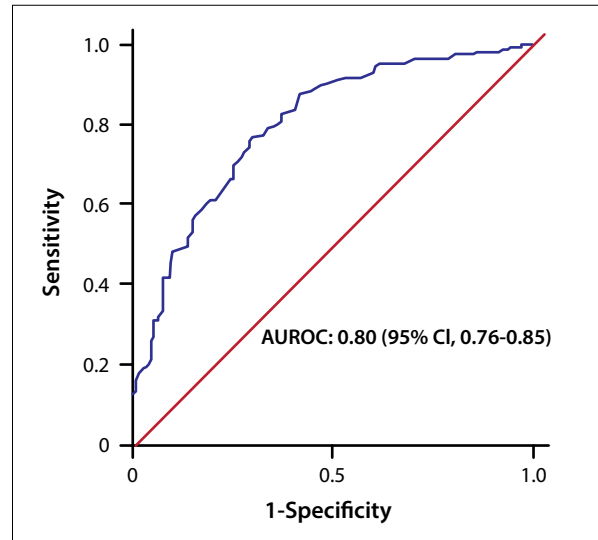

Figure 5. Sensitivity of the FAST score. AUROC, area under receiver operating characteristic curve. Adapted from Newsome PN et al. *Lancet Gastroenterol Hepatol.* 2020;5(4):362-373.[21]

suggest that a reduction of approximately half a point correlates to improvement in fibrosis, but validation is needed.

A value higher than approximately 830 msec for the multiparametric MRI cT1 platform is linked to negative outcomes over time.[28] These data are preliminary and require further validation. This cutoff value may change. However, it would be exciting to have an imaging study that could be administered at baseline and predict disease outcome 5 or 10 years later.

Applying Results to Clinical Care

Currently, the best way to use noninvasive tests is for their negative predictive value. These tests can identify patients who are at low risk (at that point in time). Physicians can use a test in the clinic's armamentarium to identify patients who are not at risk, meaning those patients who do not have NASH with moderate fibrosis. It is helpful to perform multiple tests to decrease or eliminate the indeterminate range. A wet biomarker, such as AST, can be combined with an imaging biomarker, such as FibroScan®.

These tests should be repeated, but the frequency is driven by reimbursability. Not all insurance companies reimburse to the same degree. For example, FibroScan® can be administered every 6 months based on reimbursability (although the reimbursement rate is not very high for a FibroScan®). It is reasonable to administer noninvasive tests every 6 months to 1 year, particularly in patients with high-risk features, such as diabetes, metabolic syndrome, or Hispanic ethnicity. Potentially, the interval can be longer for patients at low risk. Research from small datasets suggest that African Americans are at very low

risk for disease progression.[29] Although African Americans have high degrees of metabolic syndrome, they tend to be more protected from more advanced disease.

Disclosures

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Evolving Strategies for the Management of Nonalcoholic Steatohepatitis (NASH)

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NAFLD refers to a spectrum of diseases that can be broadly subdivided into 2 subtypes: nonalcoholic fatty liver (NAFL), the nonprogressive subtype of NAFLD; and NASH, the progressive subtype of NAFLD.[1] NASH can progress to progressive liver disease, leading to advanced fibrosis and cirrhosis. Patients may require liver transplant. NASH can also lead to hepatocellular carcinoma.

Diet and Lifestyle Management Strategies

Current management strategies reflect the stage of disease. Diet and lifestyle modifications are important across the spectrum of disease in patients with NAFLD. A low-carbohydrate diet is typically recommended for patients who are overweight or obese, or who have type 2 diabetes. For patients who are obese or overweight, the goal is a weight loss of 5% to 10%,[2] typically achieved through a diet that incorporates caloric restriction, reduced free sugar and simple carbohydrates, and increased complex carbohydrates and proteins. The Mediterranean diet, which is useful across a spectrum of metabolic diseases,[3] is typically recommended. There is some evidence to suggest that the Mediterranean diet is helpful in reducing overall cardiometabolic risk in patients with NAFLD.[4] However, no randomized, controlled trials show that one diet is better than another in improving the histologic features of steatohepatitis.

Exercise recommendations are drawn from the US Department of Health and Human Services. I recommend that patients engage in 30 to 45 minutes of moderate-intensity exercise 3 to 5 times a week. Many newly diagnosed patients have a sedentary lifestyle, and it may be difficult for them to begin an exercise program with this intensity and frequency. I recommend that patients start gradually and increase to a level of moderate intensity over 3 to 6 months, as they gradually reach the endurance to achieve 30 to 45 minutes of moderate-intensity exercise.

Weight loss can reverse disease progression.[5] A weight loss of 10% can lead to a significant reduction—or even an improvement—in fibrosis (Figure 6),[5] as well as resolution of NASH. Research has shown that it is difficult to achieve a weight loss of 10%. Maintenance of any weight loss is an important barrier.[6] Physicians are focusing on new pharmacologic weight loss therapies for patients who have high-risk NASH (as defined by a biopsy showing stage 2 fibrosis or higher).[2]

A subset of patients with cirrhosis and decompensated cirrhosis may require a liver transplant. NASH-related liver disease is now the second-leading indication for
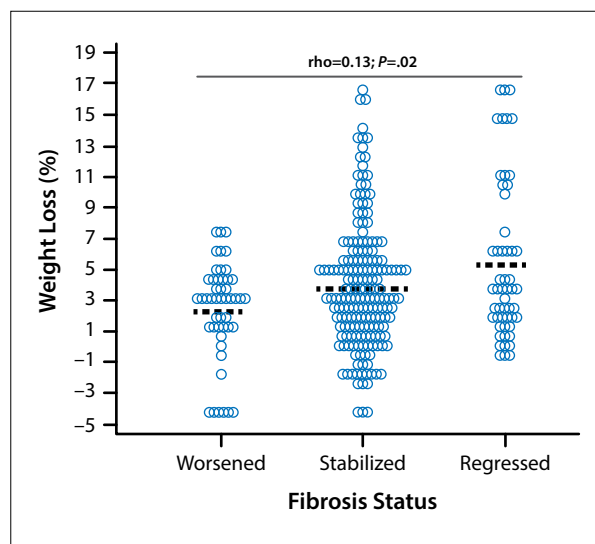

Figure 6. The relationship between weight loss and fibrosis status among patients with nonalcoholic steatohepatitis. Adapted from Vilar-Gomez E et al. *Gastroenterology.* 2015;149(2):367-378.[5]

liver transplant in the United States.[7] NASH-related liver disease is also the leading cause for the rising rates of hepatocellular carcinoma in Western countries,[8] which is thought to be due to NASH-related cirrhosis. Better therapies will reduce the risk of progression, thereby decreasing the number of patients needing transplant related to NASH, as well as the cases of NASH-related hepatocellular carcinoma.

Based on practice guidelines from the American Association for the Study of Liver Diseases (AASLD), patients with biopsy-proven NASH may be treated with vitamin E at 800 units daily.[9] This recommendation is based on data from the PIVENS trial (Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients With Nonalcoholic Steatohepatitis).[10] Vitamin E can improve steatohepatitis, ALT, and AST. There are certain caveats

> Better therapies will reduce the risk of progression, thereby decreasing the number of patients needing transplant related to NASH, as well as the cases of NASH-related hepatocellular carcinoma.

associated with vitamin E use. Vitamin E can increase the risk of hemorrhagic stroke or cardiovascular disease,[11,12] mainly due to certain bleeding tendencies associated with high doses. There is also a small risk that vitamin E will increase the risk of prostate cancer.[13] Therefore, we typically recommend the use of vitamin E in patients with well-controlled hypertension, who do not have a high risk for developing hemorrhagic stroke. Vitamin E can prevent ischemic stroke.[14]

Another option that has been considered in a small subset of patients is pioglitazone. Pioglitazone may improve NASH, and, based upon evidence from a meta-analysis, may also lead to some improvement in hepatic fibrosis.[15] Data are limited, however. Pioglitazone is typically used in the setting of type 2 diabetes. A disadvantage is that pioglitazone is associated with weight gain. It is counterintuitive to prescribe a drug associated with weight gain to patients with NAFLD and NASH, who are counselled to lose weight. The associated weight gain can be frustrating for patients. There is also a small risk of

bone density decline with pioglitazone; patients must be monitored for this event. The clinical use of pioglitazone is therefore limited.

Currently, there is no therapy recommended for patients with NASH-related cirrhosis. In these patients, management typically consists of monitoring for complications related to decompensation of cirrhosis. This approach now applies to every patient with NASH, based on a recent American Gastroenterological Association Best Practice Advice Guideline that I wrote with Hashem El-Serag, MD, MPH and colleagues.[16] We recommend that patients with NASH-related cirrhosis undergo an imaging study, with or without alpha-fetoprotein testing, every 6 months. Patients with features related to portal hypertension may benefit from endoscopy, which can be administered every 1 to 3 years. Patients should undergo periodic monitoring that incorporates laboratory testing and clinical assessment of hepatic decompensation to identify ascites or hepatic encephalopathy. These complications can be treated based on AASLD Practice Guidelines for Management of Complications of Cirrhosis.[17,18]

Most NASH patients present early in the disease course, when they are asymptomatic. When symptoms do appear, they can include fatigue and vague right upper quadrant pain that is typically unrelated to steatohepatitis disease activity. Patients with cirrhosis and decompensated cirrhosis may present with associated symptoms and complications, such as portal hypertension. These patients should be managed according to current guidelines. In addition, the majority of patients with NAFLD should be evaluated for dyslipidemia, and statins should be used if indicated. Other comorbidities associated with NAFLD include hypertension, diabetes, obesity, hypertriglyceridemia, hypothyroidism, obstructive sleep apnea, and polycystic ovarian syndrome. All these metabolic risk factors should be carefully assessed by history, physical examination, and, when appropriate, with laboratory testing. These prevalent comorbid conditions should be promptly diagnosed and appropriately treated.

Phase 3 Study Data

Several phase 3 programs are evaluating management strategies of NASH. The phase 3 REGENERATE trial (Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment) is comparing obeticholic acid vs placebo.[19] This phase 3 trial was prompted by the histologic response associated with obeticholic acid in the phase 2b FLINT trial (The Farnesoid X Receptor [FXR] Ligand Obeticholic Acid in NASH Treatment Trial).[20] The FLINT trial was conducted by the NASH Clinical Research Network
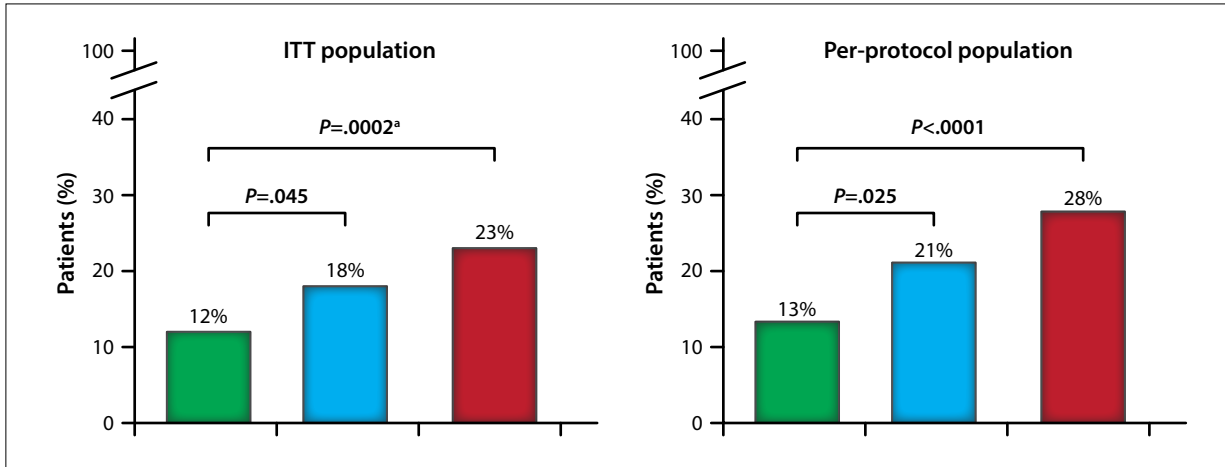
Figure 7. Improvement in fibrosis with no worsening of NASH after 72 weeks of treatment among patients in the phase 3 REGENERATE trial, which compared obeticholic acid vs placebo among patients with NAFLD and fibrosis. [a]Versus placebo. ITT, intention-to-treat; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. Adapted from Younossi ZM et al. *Lancet.* 2019;394(10215):2184-2196.[19]

in the United States. Enrolled patients had biopsy-proven NASH, with or without type 2 diabetes, without cirrhosis. The trial randomly assigned 283 patients to 72 weeks of treatment with obeticholic acid (25 mg) or placebo. Liver histology outcome was reported for 110 patients in the obeticholic acid arm and 109 patients in the placebo arm who were meant to have biopsies at baseline and 72 weeks. Improved liver histology was found in 45% of patients treated with obeticholic acid vs 21% of patients treated with placebo (relative risk, 2.2; 95% CI, 1.4-3.3; *P*=.0002). Obeticholic acid was more likely to improve fibrosis by at least 1 stage (*P*=.004). Patients treated with obeticholic acid were more likely to have a 2-point improvement in the NAFLD Activity Score.

REGENERATE is a large, international, multicenter phase 3 trial conducted across 4 continents.[19] Enrolled patients had an NAFLD activity score of at least 4 and fibrosis (stages 1 to 3). Patients with stage 1 fibrosis were enrolled only if they had at least 1 accompanying morbidity. The trial had 3 arms: obeticholic acid at 25 mg, obeticholic acid at 10 mg, and placebo. All patients received treatment for 72 weeks. There were 2 prespecified, co–primary outcomes: improvement in fibrosis by 1 stage without worsening of NASH, and NASH resolution without worsening of fibrosis.

After 72 weeks of treatment, the endpoint of fibrosis improvement was met by 12% in the placebo arm, 18% in the 10-mg obeticholic acid arm (*P*=.045), and 23% in the 25-mg obeticholic acid arm (*P*=.0002; Figure 7).[19] The frequency of serious adverse events was similar across the study arms (Table 1). Obeticholic acid may therefore improve hepatic fibrosis in patients with NASH-associated fibrosis. For accelerated approval under the US Food and

Drug Administration Subpart H, the trial had a histologic endpoint at week 72. Investigators are still monitoring patients to assess long-term clinical outcomes. Patients with NASH and cirrhosis are being evaluated in a separate trial, known as REVERSE (Study Evaluating the Efficacy and Safety of Obeticholic Acid in Subjects With Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis).[21]

Table 1. Adverse Events in the REGENERATE Trial

Events	Obeticholic Acid 10 mg (n=407)	Obeticholic Acid 25 mg (n=404)	Placebo
Pruritis (%)	28	51	19
Deaths[a] (n)	0	1	2
Gallstone-related events (%)	1	3	<1
Pancreatitis (%)	<1	<1	<1
Hepatic serious adverse events	<1	<1	<1
Cardiovascular adverse events (%)	7	6	5
- Serious adverse events (%)	1	2	2

[a]Deemed unrelated to study drugs.
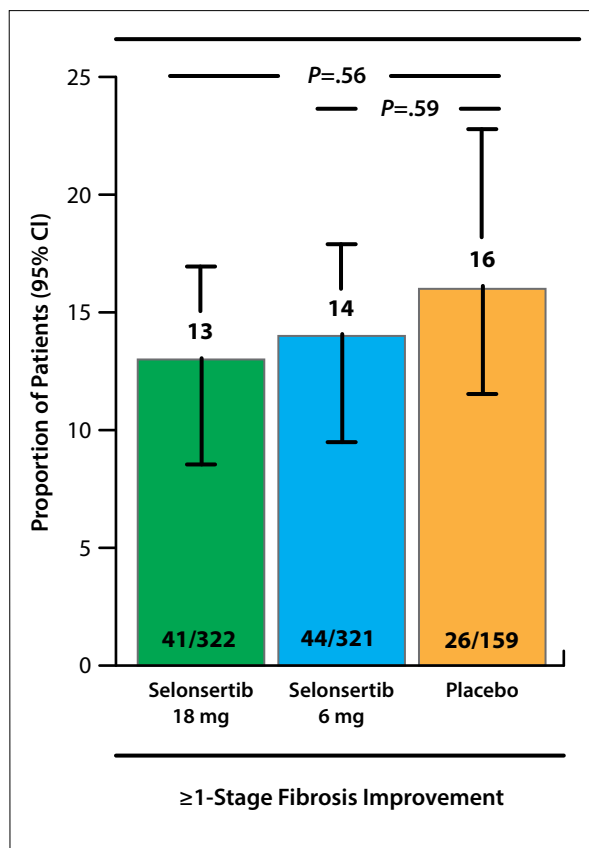Adapted from Younossi ZM et al. *Lancet.* 2019;394(10215):2184-2196.[19]

Figure 8. Selonsertib did not improve outcome vs placebo in the STELLAR-3 trial of patients with NASH and bridging fibrosis. NASH, nonalcoholic steatohepatitis. Adapted from Harrison SA et al. *J Hepatol.* 2020;73(1):26-39.[23]

Other Agents Under Investigation

Resmetirom is a thyroid hormone beta receptor agonist. The MAESTRO-NASH trial (A Phase 3 Study to Evaluate the Efficacy and Safety of MGL-3196 [Resmetirom] in Patients With NASH and Fibrosis) is comparing resmetirom vs placebo.[22] Recent trials compared selonsertib vs placebo in patients with bridging fibrosis or compensated cirrhosis due to NASH (Figure 8).[23] The trial showed no benefit to treatment. The phase 3 RESOLVE-IT study (Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis [NASH]) of elafibranor was recently terminated due to lack of efficacy.[24]

Conclusion

As Dr Anstee mentioned, rising rates of obesity are driving increased cases of NASH.[25] Among patients with NASH, fibrosis is an important indicator of progression. In studies, fibrosis is linked to long-term negative outcomes, including liver-related sequelae, cardiovascular disease, and all-cause morbidity and mortality.[26] Early identification of fibrosis can improve outcome by preventing progression to cirrhosis and consequent symptoms and comorbidities.

Although biopsy has been the traditional approach to assessing disease severity in NASH, this procedure can be burdensome for patients. In addition, inter- and intra-observer variability may impact accuracy. Dr Harrison's discussion highlights the many noninvasive tests now available for patients with NASH. The use of noninvasive testing is evolving, but it will likely be used to help diagnose and identify NASH with fibrosis, stage fibrosis, monitor treatment, and assess long-term prognosis. It is expected that pharmaceutical treatments will be available for NASH in the near future. Noninvasive testing could help guide decisions regarding management. Biochemical biomarker tests include NIS4, the NFS, the FIB-4 score, and the APRI test. Imaging tests include VCTE, MRE, and multiparametric MRI. Accuracy is increased when tests are used in combination or sequentially. Testing can be administered throughout the management course.

There are data to support lifestyle interventions for the management of NASH and NASH-related fibrosis. Exercise is recommended for patients who are able to tolerate it, and weight loss should be an early goal. Many patients with high-risk NASH, such as those with NASH stage 2 fibrosis or higher, may require pharmacologic therapies. There are now phase 3 trial data for obeticholic acid, from the REGENERATE trial.[19] In this ongoing study, patients treated with obeticholic acid were more likely to meet the endpoint of fibrosis improvement vs those treated with placebo. The REVERSE study is evaluating obeticholic acid in patients with NASH and cirrhosis.[21] Several ongoing studies are evaluating novel agents in NASH. It is expected that the role of noninvasive testing in NASH will expand as new therapies become available in this setting.

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Noninvasive Tests (NITs) in the Management of Nonalcoholic Steatohepatitis (NASH): Q&A Discussion

Stephen A. Harrison, MD, Quentin M. Anstee, BSc(Hons), MB BS, PhD, MRCP(UK), FRCP, and Rohit Loomba, MD, MHSc

Dr Stephen A. Harrison In your clinical practice, do you use a simple biochemical test or a simple imaging modality for their negative predictive value? Or do you use these tests to identify patients with disease?

Dr Quentin M. Anstee These questions are key. The use of tests likely varies across health care systems. It is necessary to consider the situation in which the test is being used. This speaks to the concept of pretest probability, and the likelihood that a particular population has the target condition. For example, a testing strategy that works well in a primary care setting may not be optimal for a secondary or tertiary care liver clinic, or for a diabetologist's office. That is something that we looked at, for example, with PRO-C3,

when we modeled how the ABC3D and FIBC3 tests would perform across a range of disease prevalences, such as 5%, 10%, and so on, for the target condition.[1] We have also looked at the ELF test in the same way, demonstrating that the positive predictive value of the test is limited at prevalences of advanced fibrosis that are likely to be encountered in primary care settings.[2]

In my practice, we start with a simple score like the FIB-4, which has a high negative predictive value. When faced with a large population that is potentially at risk, use of a simple score allows me to confidently identify patients who are unlikely to have significant fibrosis. Our second-line test is FibroScan®, which is administered to reduce the indeterminate zone in FIB-4.

It is worth noting that the patient's age can also affect how tests like FIB-4 perform.[3] For the FIB-4 test, we use the lower threshold (a cutoff of 1.3) in patients younger than 65 years. Sensitivity and specificity models show that this cutoff level overestimates disease among patients older than about 65 years. For these patients, we use a threshold of 2. This threshold triggers primary care physicians to refer patients to specialist hepatology services, where FibroScan® is used for further stratification.

Dr Stephen A. Harrison That is a great point, Dr Anstee. For at-risk NASH patients or at-risk patients with type 2 diabetes, I perform a general evaluation for common liver disease and test for viral hepatitis, talk about alcohol use, and review over-the-counter recreational drugs that are associated with liver toxicity. I also obtain some baseline liver laboratory tests, such as ALT and AST. In the absence of other liver disease, I administer a noninvasive test, such as FIB-4, followed, when indicated, by FibroScan®. What cutoff value triggers further workup or management of liver disease?

Dr Quentin M. Anstee We use a cutoff of 8.5 kPa. Obviously, interpretation of test results should be tailored to the individual patient. There is an element of judgment.

Dr Rohit Loomba I follow a similar approach, although there might be slight differences in the cutoff points. I am conducting a prospective study in patients with type 2 diabetes. Patients undergo systematic screening after referral by their primary care physicians. It appears that the high-risk patients are age 50 years and older. The FIB-4 cutoff of 1.3 may miss some patients, so I have reduced that cutoff to 1. A FIB-4 score below 1 indicates low risk, and these patients can undergo follow-up without immediate intervention. Based on data from Dr Anstee,[4] if a patient has a FIB-4 score of 2.67 or higher, but lacks overt signs of cirrhosis, I perform a biopsy. I do not perform another noninvasive test just for the sake of further risk-stratifying a patient with a score above 2.67. In rare cases, there may

be an indication that another unusual factor is increasing the FIB-4 score, and further testing would be warranted. However, if a patient is unlikely to have liver disease, a biopsy may not be needed. Their risk of having significant disease is already 40%. A second test, such as FibroScan®, MRE, or ELF, is needed only when the FIB-4 score is between 1 and 2.67. An MRE higher than 2.55 kPa suggests NASH, and an MRE higher than 2.99 kPa suggests fibrotic NASH. Among patients with an MRE of 3.3 kPa or higher and a FIB-4 score of 1.6 or higher, the positive predictive value for NASH with stage 2 fibrosis or higher exceeds 90%. (This is the important derivation from new data from our group.)

At my institution, the available tests are FibroScan® and MRE. A concern with FibroScan® is that it may lack precision. As an example, I have a patient with cirrhosis who had a FibroScan® test result of 6.9 kPa. I have many patients with significant fibrosis whose test results are around 7 kPa. Therefore, I use slightly lower cutoffs for the next tests for such patients. I use a cut point of 1.6 for FIB-4 and of 7.6 kPa for FibroScan®. These values are derived from my own prospective research, and they are tailored to my practice. But I agree with you: For a patient with a FibroScan® result of 8.5 kPa or higher, I would proceed with a biopsy followed by enrollment in a clinical trial.

Dr Stephen A. Harrison We agree that there is not one single test that we use for subsequent treatment decisions. We tend to employ sequential combination testing, with the goals of decreasing the indeterminate nature of these tests and improving their overall accuracy.

I like the idea of the FAST score. I use the AST level in my clinical practice, and this level is the biggest component of FIB-4, as well. The FAST score combines FibroScan® with AST, and an app is available to calculate the score.[5] There are different ways to approach testing. Sequential combination testing, including a wet biomarker with an imaging biomarker, is probably the best approach.

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Slide Library

Early Detection of Fibrosis in Nonalcoholic Steatohepatitis (NASH)

- Fibrosis has consistently been identified as the condition that best predicts long-term outcomes, including liver-related sequelae, cardiovascular disease, and all-cause morbidity and mortality[1]
- It is beneficial to identify patients with fibrosis, even at relatively early stages
- Intervening in a timely manner could prevent subsequent progression to cirrhosis, and consequent worsening of symptom burden and morbidity
- Early detection of fibrosis is beneficial for patients with fatty liver, and will remain an important underpinning feature of management

1. Taylor RS et al. Gastroenterology. 2020;158(6):1611-1625.e12.

Assessing Disease Severity in NASH

- The classic approach to assessing disease severity in NASH is with liver biopsy, but this invasive procedure has several limitations
- Noninvasive tests can be divided into 2 broad categories: biochemical biomarkers and imaging biomarkers
  - Biochemical biomarker tests include NIS4, the NAFLD fibrosis score (NFS), the FIB-4 score, and the aspartate transaminase to platelet ratio (APRI) test
  - Imaging tests include vibration-controlled transient elastography (VCTE), magnetic resonance elastography, and multiparametric magnetic resonance imaging

NAFLD, nonalcoholic fatty liver disease.

Noninvasive Tests in NASH

- Accuracy is improved when the tests are used in combination or sequentially, by decreasing the proportion of patients with indeterminate values
  - A wet biomarker, such as aspartate transaminase, can be combined with an imaging biomarker
- It is reasonable to administer noninvasive tests every 6 months to 1 year, particularly in patients with high-risk features

Noninvasive Testing in NASH: Current and Future Applications

- To diagnose and identify NASH with fibrosis, as well as to stage fibrosis
- For treatment monitoring. There will likely be pharmaceutical treatments for NASH in the near future. Noninvasive testing could determine how well the drug is working, and help guide decisions regarding whether the drug should be stopped or continued, with or without dose modification
- To assess long-term prognosis. It may be possible to perform a simple test that will predict a patient's risk for a negative outcome in 5 or 10 years

Management of NASH

- Current management strategies reflect the disease stage
- Diet and lifestyle modifications are important across the spectrum of disease
  - A weight loss of 10% can lead to a significant reduction—or even an improvement—in fibrosis[1]
- Phase 3 study data are now available for obeticholic acid[2]
- Trials of other pharmaceutical agents are ongoing

1. Montesi L et al. Diabetes Metab Syndr Obes. 2016;9:37-46. 2. Younossi ZM et al. Lancet. 2019;394(10215):2184-2196.

Phase 3 Data for Obeticholic Acid in NASH

- The ongoing phase 3 REGENERATE trial is comparing obeticholic acid vs placebo
- Enrolled patients have an NAFLD activity score of at least 4 and fibrosis (stages 1 to 3). Patients with stage 1 fibrosis have at least 1 accompanying morbidity
- After 72 weeks of treatment, the endpoint of fibrosis improvement was met by 12% of patients in the placebo arm, 18% in the 10-mg obeticholic acid arm (P=.045), and 23% in the 25-mg obeticholic acid arm

REGENERATE, Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment; Younossi ZM et al. Lancet. 2019;394(10215):2184-2196.

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