MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

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Utilization of Noninvasive Tests to Diagnose At-Risk Metabolic Dysfunction-Associated Steatohepatitis

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G&H Why is it important to diagnose at-risk metabolic dysfunction-associated steatohepatitis?

MN Metabolic dysfunction-associated steatohepatitis (MASH; formerly known as nonalcoholic steatohepatitis) is prevalent in the United States but is frequently underdiagnosed. Several studies have demonstrated that MASH with a fibrosis stage of 2 and higher, which is known as at-risk MASH, has a correlation with morbidity and mortality. In other words, stage 2 fibrosis appears to be the tipping point where the risk of morbidity and mortality starts significantly increasing. Regulatory authorities such as the US Food and Drug Administration and the European Medicines Agency have endorsed at-risk MASH patients as the group of MASH patients to target for pharmacologic therapy. Therefore, it is important to identify these patients so they can be treated correctly and be entered into appropriate clinical trials.

G&H What are the challenges of diagnosing these patients?

MN MASH can be complex to diagnose because it involves the evaluation of steatosis, fibrosis, and inflammation in the liver. Although steatosis as well as fibrosis historically have been very well characterized, especially on imaging studies, it has been particularly challenging to identify inflammation in patients with MASH. Recent efforts have led to the development of composite scores using various noninvasive tests (NITs) along with other clinical parameters. These scores can predict the spectrum from steatohepatitis to fibrosis. Composite scores have included parameters such as hemoglobin A1C, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and the Fibrosis-4 (FIB-4) score as well as patient demographic information, which make it easier to predict steatohepatitis, the driver of the disease.

It is also important to note that although liver biopsy is the reference standard that these scores are compared against, it has many limitations, including sample variabilities and inter- and intraobserver disagreements.

G&H Which NITs have the most supporting evidence for utilization in the diagnosis of at-risk MASH?

MN The American Association for the Study of Liver Diseases (AASLD) recently released its first guidance endorsing multiple NITs for the identification of at-risk MASH. All of these are imaging-based composite scores with laboratory components. One NIT is called the FAST score, which stands for FibroScan (Echosens; transient elastography) plus AST. This score is based on 3 values: the controlled attenuation parameter measurement from FibroScan, which reflects steatosis; the liver stiffness measurement from FibroScan, which reflects fibrosis; and the AST laboratory value, which reflects inflammation. This score is thought to identify at-risk MASH with a high sensitivity of 0.35 and high specificity of 0.67. The score is considered to be continuous because it produces a number from 0 to 1. A similar score that is also continuous is the MAST score. This score replaces transient elastography with magnetic resonance imaging (MRI)-based

evaluation that includes MRI–proton density fat fraction (PDFF) plus magnetic resonance elastography (MRE) plus AST. It has 2 cutoff values with high sensitivity and high specificity for identifying MASH stage 2 and higher.

Another NIT is the MEFIB test, which is dichotomous rather than continuous because it rules in or out MASH. The MEFIB test uses both MRE and the FIB-4 score. This test has also identified MASH stage 2 fibrosis and higher. There have been attempts to compare the MAST and MEFIB scores, but these comparisons have only been done by the original authors of the scores. Overall, the MAST score has shown better correct classification than the MEFIB score, but validation from outside cohorts is needed.

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There has also been research on multiparametric MRI (cT1), but this test needs more clarification and validation. It is not yet ready for use in identifying at-risk MASH.

G&H Which nonimaging-based tests have been the most promising in the detection of at-risk MASH?

MN Because transient elastography and MRI are not widely available, there has been a movement toward identifying at-risk MASH using composite scores (mainly ALT, AST, platelet count, hemoglobin A1C, and patient characteristics such as body mass index, age, and sex). One such test was NIS4, which was recently modified and changed to NIS2+. A recent article in the *Journal of Hepatology* compared the 2 tests and found that NIS2+ had an improved performance for identifying at-risk MASH.

Excitingly, a study on the metabolomics advanced steatohepatitis fibrosis (MASEF) score was recently published in *Hepatology*. This score, which includes 12 lipids in addition to other parameters such as liver enzymes, detected MASH stage 2 fibrosis and higher better than the FAST score. The study also compared the current screening guidelines, FIB-4 followed by transient elastography, with FIB-4 followed by the MASEF score. The 2 combinations had similar results. These are important findings because transient elastography is not available everywhere. In contrast, this metabolomics test will be commercially available to order soon anywhere in the United States. In addition, transient elastography, which is recommended in recent guidelines, looks only at liver stiffness rather than at-risk MASH (ie, MASH in fibrosis stage 2 and higher), whereas the MASEF score looks at MASH in fibrosis stage 2 and higher.

In summary, there are now 3 combinations of imaging and serum blood tests endorsed by the AASLD to diagnose at-risk MASH, and there are also 2 serum-based tests with other parameters that can be used to define at-risk MASH. There has been a significant evolution in diagnosis over the past year and a half.

G&H How can these scores be calculated?

MN There was some initial concern that the tests may be difficult to use. Some physicians were a bit intimidated at first by the FAST or MAST scores and felt somewhat overwhelmed by the amount of data coming out for the different tests. However, it is good to have supporting data, and there are websites or apps that can calculate these scores. For example, CouldItBeNASH.org includes the formulas for the MAST score (-12.17 + 7.07 log liver stiffness measurement + 0.037 PDFF + 3.55 log AST) and MEFIB score (MRE ≥3.3 kilopascals and FIB-4 ≥1.6 rules in at-risk MASH). Physicians just need to enter the values for the score components, and the scores are calculated immediately.

The serum tests that will become available soon have simplified the process even further, as physicians do not need to calculate the scores; physicians just receive the scores from the laboratory.

G&H Which of these NITs do you typically use in clinical practice, and how has your experience been with them?

MN I have used the FAST and MAST scores. I usually use them alternately; however, the MAST score has been proven to be more accurate, especially in clinical trials, and it is often used in large clinical centers. On the other hand, the FAST score is easier to use, as FibroScan can be done in hepatology and gastroenterology offices. It is probably the most widely used NIT in these offices at the current time.

NIS2+ and MASEF are not commercially available yet. I am not sure when NIS2+ will be available, but I

do know that MASEF will be available commercially this year. I have used this score through my research and think physicians will be excited about it when it comes out.

> MASH is probably the last liver disease that relies on biopsy, and many other types of diseases do not use biopsies anymore.

G&H Do you think these NITs will become widely used and will eventually replace liver biopsy?

MN They should because liver biopsy is invasive and associated with a number of challenges and risks, even though it is currently the reference standard for diagnosing at-risk MASH. In addition, patients do not like undergoing the procedure. MASH is quite prevalent, and it would be irresponsible to keep biopsying patients over the long term. MASH is probably the last liver disease that relies on biopsy, and many other types of diseases do not use biopsies anymore. For example, lung biopsies, heart biopsies, and prostate biopsies are not being used any longer. It is time for MASH to be updated and to look into a future without liver biopsy. Regulators may be hesitant to move forward with clinical trials without liver biopsy, but I encourage them to do so, as this would help advance the field.

G&H What further research is needed in this area?

MN These NITs should be used in patients who are referred to hepatology providers to determine whether treatment with pharmacologic agents is needed. More data are required to confirm that real-world findings are consistent with clinical trial findings and to enter these patients into clinical trials for at-risk MASH. It is now known that these NITs can be used at baseline to identify these patients. Whether these tests are helpful longitudinally or not is still being studied.

It is also important to correlate all of these at-risk MASH scores with outcomes data. Data now show that the FAST, MAST, and MEFIB scores correlate with clinical outcomes, but we need to show that the NIS2+ and MASEF serum tests correlate with outcomes as well. Most important is to determine whether these tests predict response to therapy, although this has been difficult to determine because we do not have drugs that are effective yet. There are also a number of other ongoing and upcoming studies on at-risk MASH; there is constant discussion about this topic.

Disclosures

Dr Noureddin has served on the advisory board of 89bio, Altimmune, BI, CytoDyn, GSK, Madrigal, Merck, Novo Nordisk, Terns, and Takeda; has been principal investigator for a drug study for Allergan, Akero, BMS, Gilead, Galectin, Genfit, GSK, Conatus, Corcept, Enanta, Madrigal, Novartis, Novo Nordisk, Shire, Takeda, Terns, Viking, and Zydus; and has been a stockholder of Rivus Pharmaceuticals, CIMA, CytoDyn, and ChronWell.

Suggested Reading

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