NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

Section Editor: Stephen A. Harrison, MD

Current Understanding of Risk for Nonalcoholic Steatohepatitis and Progressive Fibrosis

Mazen Noureddin, MD, MHSc
Director, Cedars-Sinai Fatty Liver Program
Division of Digestive and Liver Diseases
Comprehensive Transplant Center
Cedars-Sinai Medical Center
Los Angeles, California

G&H What is the natural history of nonalcoholic steatohepatitis?

MN Nonalcoholic steatohepatitis (NASH) is part of the disease spectrum of nonalcoholic fatty liver disease (NAFLD). The first step of this spectrum is nonalcoholic fatty liver, which is simple steatosis (ie, fat accumulation in the liver). This condition occurs in approximately 25% of the general population. Approximately 10% to 20% of these patients progress to the more advanced form of the disease, which is NASH with or without fibrosis. In addition to fat accumulation, NASH consists of cellular injury manifested by cell ballooning and inflammation. NASH drives fibrosis that may progress over time into cirrhosis or even to hepatocellular carcinoma.

G&H Which demographic variables put patients at increased risk for NASH and progressive fibrosis?

MN The most significant risk factor in terms of demographics is metabolic syndrome. Dyslipidemia, hypertension, obesity, and type 2 diabetes (T2D) have been shown to be associated with NAFLD in its more advanced form. In particular, T2D is a significant risk factor for the advanced form of NAFLD as well as fibrosis. For example, it has been shown that approximately 60% of patients with T2D have NAFLD, and almost 10% of those patients have advanced fibrosis. One of the most noteworthy studies on this issue was conducted by Dr Stuart McPherson and colleagues in 2015. They followed 108 NAFLD patients longitudinally with liver biopsies for a median interval of 6.6 years and found that T2D was a risk factor for advanced NAFLD and fibrosis.

G&H Which laboratory data are associated with more advanced fibrosis?

MN There are traditional laboratory tests that are used to determine the advancement of fibrosis, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and, specifically, the AST/ALT ratio. Doctors have also historically looked at platelet counts, especially their slope and trend over time. Once patients start developing thrombocytopenia, there is a concern that patients with NAFLD may have cirrhosis. Similarly, low albumin and high bilirubin point toward the likely presence of cirrhosis. Given the practical use of laboratory tests, scores have been developed to assess the presence of advanced fibrosis with higher accuracy, such as the Fibrosis-4 (FIB-4) score and the NAFLD fibrosis score (NFS). These scores are based on liver enzymes, platelet count, and age, and in the case of the NFS, T2D status is also included. These scores have been shown to have very good specificity for the assessment of advanced fibrosis. A meta-analysis published in 2011 by Dr Giovanni Musso and colleagues studied 3000 patients and found that the area under the receiver operating characteristic curve for the NFS was

0.85 for assessing advanced fibrosis. Many studies on the FIB-4 score have found similar values.

G&H Which histopathologic criteria are associated with progressive disease?

MN This has been one of the most important and hottest topics in NASH over the past 5 years. A 2015 study by Dr Paul Angulo and colleagues showed that histologically, fibrosis is the most predictive factor for transplant-free survival. In 2017, Dr Hannes Hagström and colleagues examined a European cohort of 646 patients with baseline biopsies and looked at their complications, especially liver-related events and mortality, over a mean follow-up period of 20 years. Fibrosis, especially starting at stage F2 and higher, predicted the poorest outcome in terms of liver-related events. In the same year, a meta-analysis by Dr Parambir Dulai and colleagues confirmed that patients have higher mortality at stage F2 and higher.

> … the highest risk for advanced fibrosis is a patient with multiple comorbidities such as T2D, obesity, hypertension, and dyslipidemia who is above a certain age (eg, >40 years) and who has an NFS or FIB-4 score that is elevated.

G&H How can these variables be combined to determine which patients are the most likely to have NASH and progressive fibrosis?

MN As discussed, metabolic syndrome, especially T2D, is an important risk factor for NASH and advanced fibrosis, and fibrosis stage is predictive of a worse outcome. In general, the more risk factors a patient has, the more likely it is that he or she has advanced fibrosis. Thus, the highest risk for advanced fibrosis is a patient with multiple comorbidities such as T2D, obesity, hypertension, and dyslipidemia who is above a certain age (eg, >40 years) and who has an NFS or FIB-4 score that is elevated. This risk can be confirmed via biopsy or noninvasive testing. If confirmed, the patient is at increased risk of morbidity and mortality, and makes up the targeted population for clinical therapies and trials.

G&H How should the patients at greatest risk be managed?

MN Advanced fibrosis is very important, as patients with this condition are at risk of progressing to cirrhosis soon. For example, a study by Dr Arun Sanyal and colleagues in 2019 showed that patients with stage F3 disease (ie, precirrhosis) can progress to cirrhosis very quickly; approximately 1 in 5 patients progressed from stage F3 to F4 within 2.5 years. That is a very significant finding that can be used as a strategy to determine treatment. Overall, patients can be divided into those with significant and advanced fibrosis and those without fibrosis. For all patients, weight loss and exercise should be the backbone of therapy. For patients with no advanced fibrosis, weight loss and exercise will probably be the only treatment.

Weight loss can be achieved via many methods, such as various diets. The Mediterranean diet has been studied the most in terms of NAFLD and NASH, but newer data show that the low-carbohydrate diet and possibly intermittent fasting are helpful as well. In addition, the type of food eaten is important. For example, my colleagues and I published an article this year that showed that red meat and chicken are associated with the risk of NAFLD. Red meat and food rich with cholesterol were also associated with the risk of NAFLD cirrhosis. We also found that fiber, such as from vegetables, is protective. Dr Stephen Harrison and colleagues, as well as my colleagues and I, have published data showing that coffee has antisteatotic and antifibrotic effects. In addition, a good deal of data have been published on the role of exercise in NAFLD and NASH.

The same principles of diet and exercise should be applied to patients with advanced fibrosis. However, it is important to understand that patients with advanced fibrosis are very different from those with nonadvanced fibrosis. More is needed for patients with advanced fibrosis than just weight loss and exercise. Given the aforementioned data that some patients progress to cirrhosis within a short period of time, I urge gastroenterologists and hepatologists to offer these patients options in addition to diet and exercise, such as clinical trials and, in the future, medications. There are many promising clinical trials currently underway for patients with advanced fibrosis. It is likely that therapies may be approved by the US Food and Drug Administration in the near future. These patients also may need hepatocellular carcinoma as well as esophageal varices screening and close follow-up to try to reverse fibrosis.

G&H What has recent research found regarding the risk of NASH in African-American patients? Do they progress to cirrhosis often?

MN This is an interesting area that still needs more research. In general, African Americans are less likely to develop steatosis in the liver; therefore, much less NAFLD and NASH are seen in this population. This could be due to genetic factors, fat distribution in the body, or other factors. However, a study published in 2016 by Dr Veronica Wendy Setiawan and colleagues, of which I was a part, showed that African Americans are not spared from NAFLD or NAFLD cirrhosis. Indeed, NAFLD cirrhosis was the second leading cause of cirrhosis in African Americans in our studied cohort. In 2018, Dr Kenneth Cusi's group found that African Americans developed less fatty liver. However, once this condition occurred, the patients developed NASH as severe as other NAFLD patients, as well as fibrosis and cirrhosis.

G&H Is it known why women seem to have more advanced or progressive disease even though men have more NAFLD than women?

MN This is another intriguing area that requires more research. Estrogen is likely protective, as data seem to suggest that NAFLD may progress more quickly after menopause. The results of a meta-analysis by Dr Maya Balakrishnan and colleagues were recently published online ahead of print publication. Fifty-four studies consisting of 62,239 NAFLD patients were included, of which 5428 had NASH and 6444 had advanced fibrosis. The authors found that women were at lower risk for NAFLD than men. However, once NAFLD was established, women had a higher risk of having advanced fibrosis than men, especially at 50 years of age and older.

G&H What is the latest research on the role of genetics (eg, *HSD17B13* and *PNPLA3* mutations) on disease progression?

MN This is an important topic that is increasing in significance as more discoveries are being made. Several studies over the past 10 years have shown that the presence of *PNPLA3* and/or *TM6SF2* are associated with increased steatosis, steatohepatitis, and cirrhosis by 2- to 4-fold. Research on *HSD17B13* has been more recent. A study showed that there is an association between a loss-of-function variant in *HSD17B13* and a decreased risk of chronic liver disease as well as progression from steatosis to steatohepatitis. The best publication on this gene came from Dr Yanling Ma and colleagues last year, which revealed the association of variants in *HSD17B13* with histologic features of NAFLD and identified the HSD17B13 enzyme as a lipid droplet–associated retinol dehydrogenase. This is a landmark study in hepatology, and more research is needed on the protective role of this gene.

G&H Does the microbiome appear to play a role in the risk for NASH and progressive fibrosis?

MN The microbiome is a hot topic that is still in early stages of research in NAFLD, but there is a clear signal that the microbiome is associated with various degrees of fibrosis in NAFLD patients. For example, the microbiome in NAFLD cirrhotic patients is different than the microbiome in patients with less severe fibrosis. It was suggested by Dr Rohit Loomba's group that the microbiome can serve as a biomarker to distinguish various stages of the disease. Thus far, there have only been a few association studies in humans and mechanistic studies in animals; therefore, this area needs to be studied further.

G&H What are the priorities of research regarding the risk of NASH and progressive fibrosis?

MN More research is needed on genetics, microbiome association, mechanisms, and environmental factors such as diet and variation in geographic areas around the world. Effective therapies are in the process of being developed, as treatment constitutes the greatest unmet need in NAFLD. In addition, advancements have been made in terms of biomarkers and noninvasive testing to stage and monitor the disease, but further research is needed over the next few years on more accurate biomarkers and on how to determine the best one or the best combination. In the future, it is likely that there will be a combination of biomarkers that will be used to identify or risk stratify patients with advanced fibrosis accurately, which will allow doctors to follow these patients longitudinally. In addition, therapy will likely consist of a combination of treatments, similar to the field of T2D where doctors combine therapies to achieve the best therapeutic response.

Disclosures

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Suggested Reading

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