ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Diagnosis of Nonalcoholic Steatohepatitis Without Liver Biopsy

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G&H What is the relationship between nonalcoholic steatohepatitis and nonalcoholic fatty liver disease, and how common are these conditions?

BM Nonalcoholic fatty liver disease (NAFLD) refers to a group of conditions in which there is fat accumulation in the liver without liver cell injury in people who do not have excessive alcohol use. Nonalcoholic steatohepatitis (NASH) is an aggressive form of NAFLD in which there is associated injury to the liver cell, leading to inflammation in the form of steatohepatitis. Due to the associated steato (fatty) hepatitis, the inflammation can progress to fibrosis (stiffening of the hepatic tissue) and eventually to the irreversible stage of cirrhosis.

In the general US population, NAFLD currently has an estimated prevalence of approximately 20%. However, in the morbidly obese population, the prevalence of NAFLD is estimated to be as high as 75% to 92%, and the condition may affect up to 17% of children and adolescents.

G&H Which patients have a higher risk of NASH?

BM NASH is most frequently associated with metabolic syndrome, a disease in which patients also have diabetes, obesity, and resistance to the actions of insulin; therefore, these patients are unable to break down sugar. It is difficult to estimate the prevalence of NASH because it is asymptomatic. In the United States, when a liver biopsy is performed due to altered liver function, 3% to 5% of patients are diagnosed with NASH.

G&H How has NASH historically been diagnosed?

BM For the past 50 years, a common method for diagnosing fatty livers has been diagnostic ultrasound. The appearance of a hyperechoic liver (showing more echogenicity than the kidneys), vascular blurring, and deep attenuation on ultrasonography are consistent with liver steatosis. Liver ultrasonography has a fairly good sensitivity and specificity for detecting liver steatosis. However, the procedure is associated with significant inter- and intraobserver variability and is operator-dependent.

Liver imaging by computed tomography (CT) next became available, and it showed that a fatty liver had a lower attenuation on CT images than a normal liver. A lower hepatic attenuation of 10 HU relative to the spleen is consistent with hepatic steatosis. The most common CT method of diagnosing hepatic fatty liver disease involves the determination of liver attenuation of scans compared to that of the spleen (the liver-to-spleen attenuation difference).

The introduction of magnetic resonance (MR) in the 1990s expanded the ability to diagnose fatty liver disease via imaging. Currently, there are several types of MR sequences that allow a biochemical assessment of the liver. MR spectroscopy can detect hepatic steatosis; however, this method represents a research tool and is not available clinically for the screening of NASH or other forms of fatty liver disease. With opposed-phase imaging, it is possible to demonstrate the presence of fat in the cells of any tissue, in this case specifically hepatocytes. Opposed-phase imaging is often used in the liver and for the characterization of other fat-containing masses, such as adrenal nonfunctioning cortical adenomas. However, this method is qualitative and cannot determine the grade of hepatic steatosis.

A newer MR technique, proton density fat fraction (PDFF), determines the fat fraction in the liver. In a study conducted by researchers at the University of California

San Diego, PDFF had a sensitivity of 93% and a specificity of 85% for differentiating moderate to severe fatty changes from mild or absent forms.

G&H Has there been any other research on how accurate these imaging techniques are in terms of diagnosing NASH?

BM A study from the *World Journal of Hepatology* reviewed the accuracy of imaging techniques compared to liver biopsy. Both magnetic resonance imaging (MRI) and MR spectroscopy are very accurate and reproducible for measuring hepatic fat. In contrast, ultrasound and CT have limited accuracy for diagnosing mild hepatic steatosis and have intra- and interobserver variability. However, ultrasound is fairly accurate and has acceptable sensitivity (81.8%-100.0%) and specificity (as high as 98%) for diagnosing moderate to severe hepatic steatosis (defined as histologic degree ≥30% or 33%) in patients without coexisting liver disease.

CT is likewise fairly accurate at diagnosing moderate to severe hepatic steatosis, particularly in donor candidates for liver transplantation. Hepatic steatosis reduces the attenuation of liver parenchyma because the attenuation value of fat (approximately −100 HU) is lower than that of soft tissue. Liver ultrasonography has a sensitivity of 60% to 94% and a specificity of 88% to 95% for detecting liver steatosis.

However, none of these imaging methods can definitively differentiate fatty liver alone from NASH, nor predict the degree of liver fibrosis, which can cause progressive liver damage and other consequences.

G&H What are the advantages of using imaging techniques for diagnosing NASH?

BM One of the reasons that imaging techniques have become important is that the field of hepatology has developed agents to halt the progression of hepatitis-related fibrosis and cirrhosis, especially involving hepatitis C virus infection. Thus, it is important to identify patients who should be treated with these agents.

In addition, these imaging techniques offer an advantage to the patient over liver biopsy, which inherently has risks owing to its invasive nature. Although liver biopsies have become easy to perform under ultrasound guidance or other methods, patients who have liver disease are at risk for biopsy complications because as their liver becomes damaged, they do not have the ability to coagulate blood well and, therefore, have an increased risk of bleeding. Also, ascites is a contraindication to percutaneous liver biopsy. When ascites is present, a liver biopsy should be undertaken using a safer method—the transjugular approach.

Another advantage of imaging techniques is that they offer complete surveillance of the liver, whereas biopsies are just a sample of the liver. The distribution of fat in a liver may not be uniform; therefore, some areas of the liver may not contain any fat.

G&H What are the limitations or risks associated with the use of imaging methods for diagnosing NASH?

BM There has been a move away from using methods with radiation because cumulative radiation is considered carcinogenic by the National Institutes of Health. In addition, doctors are trying not to use CT as much as in the past because MR is available as an option. Thus, CT is not being promoted as a screening method. It is possible to screen for fatty liver disease with ultrasound because there is a large availability of ultrasound scanners in the community, and criteria for a fatty liver are widely established. As MRI continues to be refined, and as its costs decrease and its availability increases, it may replace CT in the assessment of fatty liver disease.

G&H What is the role of elastography in the diagnosis of NASH?

BM Fibrosis is the hallmark of the steatohepatitis that is present in NASH and absent in NAFLD. Elastography is a novel method to determine the presence of fibrosis in tissues without the need for biopsy. This technique measures the degree of tissue stiffness when a sound wave is transmitted through tissue and the speed of propagation is measured. Scales for grading tissue stiffness have been compared to the degree of fibrosis seen on biopsies of the liver. Elastography is performed via ultrasound or MR.

Transient elastography (Fibroscan, Echosens) and shear wave elastography, which study the speed of an ultrasound wave through tissue, have important roles in the setting of NASH. When tissue has fibrous elements, the transmission of an ultrasound wave is fast. These ultrasound elastographic methods, also known as acoustic radiation force impulse, can determine whether a liver has fibrosis. Shear stiffness values of less than 3 kPa indicate normal liver parenchyma. Thus far, most research has shown that a cutoff value of 3 kPa can help differentiate normal liver parenchyma from steatohepatitis or fibrosis.

MR elastography uses the same principles as shear wave elastography and transient elastography, but is combined with MRI. There are several potential advantages of MR elastography over ultrasound-based elastography techniques. These advantages include a larger sampling volume and fewer technical failures, especially in patients with a body mass index greater than 30.

It is important to distinguish mild (F1-F2) from advanced or severe (F3-F4) fibrosis, as patients with severe fibrosis have a greater risk of complications and need to undergo screening for hepatocellular carcinoma. When distinguishing stages F3 to F4 from F0 to F2 with 5.9 kPa as the cutoff value, MR elastography had an overall sensitivity, specificity, and diagnostic accuracy of 85.4%, 88.4%, and 87.0%, respectively.

G&H Is there still a role for liver biopsy in patients suspected of NASH?

BM The gold standard for diagnosing patients with NAFLD, especially NASH, is still considered to be liver biopsy. Biopsies of patients with NASH can demonstrate mild to moderate iron deposition in hepatocytes, Kupffer cells, and sinusoidal endothelial cells related to a typical fibrosis pattern, which cannot be seen via imaging methods.

However, it is important to note that in the past, biopsies were always needed in liver masses because of the possibility that they might develop into cancers. Currently, the imaging characteristics of tumors in the cirrhotic liver are very well established, and biopsies have become less important.

Dr Madrazo has no relevant conflicts of interest to disclose.

Suggested Reading

Castera L. Noninvasive evaluation of nonalcoholic fatty liver disease. *Semin Liver Dis*. 2015;35(3):291-303.

Cui J, Heba E, Hernandez C, et al. Magnetic resonance elastography is superior to acoustic radiation force impulse for the diagnosis of fibrosis in patients with biopsy-proven nonalcoholic fatty liver disease: a prospective study. *Hepatology*. 2016;63(2):453-461.

Dulai PS, Sirlin CB, Loomba R. MRI and MRE for non-invasive quantitative assessment of hepatic steatosis and fibrosis in NAFLD and NASH: clinical trials to clinical practice. *J Hepatol*. 2016;65(5):1006-1016.

Lee SS, Park SH. Radiologic evaluation of nonalcoholic fatty liver disease. *World J Gastroenterol*. 2014;20(23):7392-7402.

Nasr P, Forsgren MF, Ignatova S, et al. Using a 3% proton density fat fraction as a cut-off value increases sensitivity of detection of hepatic steatosis, based on results from histopathology analysis [published online March 9, 2017]. *Gastroenterology*. doi:10.1053/j.gastro.2017.03.005.

Noureddin M, Lam J, Peterson MR, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. *Hepatology*. 2013;58(6):1930-1940.

Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. *J Magn Reson Imaging*. 2011;34(4):729-749.