Can Nash Be Diagnosed, Graded, and Staged Noninvasively?

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KEYWORDS

• Nonalcoholic fatty liver disease • Nonalcoholic steatohepatitis • Noninvasive
• CK-18 • Fibrosis • Fibrogenesis • FibroScan • Magnetic resonance elastography

KEY POINTS

- Nonalcolohic fatty liver disease (NAFLD) affects a substantial proportion of the population worldwide.
- Few subjects who have the condition develop liver-related complications.
- Predicting which patients will develop progressive disease is problematic.
- Currently, there is no available noninvasive test demonstrated to be simple, reproducible, and valid for disease staging in patients with NAFLD.
- Liver biopsy remains the gold standard investigation to distinguish between patients with nonalcoholic steatohepatitis and those without NASH or bland steatosis, and to determine disease prognosis based on fibrosis staging.

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) refers to the accumulation of fat (mainly triglycerides) in hepatocytes that results from insulin resistance.[1] It is the most common chronic liver disease in the Western world. Data from the National Health and Nutrition Survey from 1988 to 2008 show that the prevalence of common chronic liver diseases has remained stable, except for NAFLD, as defined by idiopathic elevation of liver enzymes, which is increasing.[2] The clinicopathologic spectrum of NAFLD ranges from bland hepatic steatosis, which is clinically associated with a similar long-term prognosis as compared to the general population, to nonalcoholic steatohepatitis (NASH), which when associated with increased liver fibrosis, may progress to cirrhosis and liver failure. As such, distinguishing between steatosis and NASH with and without fibrosis has important implications for management and patient counseling.

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NAFLD is a growing medical problem affecting any age range, with a reported prevalence of 9.6% among adolescents and preadolescents,[3] and 34% among patients aged 30 to 65 years.[4] However, the reported prevalence of this condition varies based on the study population studied and the diagnostic modality used. For instance, liver biopsies performed in otherwise healthy potential liver donors revealed a prevalence of NAFLD (as defined by greater than 30% of steatosis) of 20%,[5] whereas studies using magnetic resonance (MR) spectroscopy reported a prevalence of 34% in the general adult population in Dallas County, Texas.[4] Studies using idiopathic elevations in liver enzymes as a case definition yielded a wide NAFLD prevalence of 8% to 75%.[6–8]

ROLE OF LIVER BIOPSY IN DIAGNOSING AND STAGING NASH

The decision regarding whom and when to biopsy should take into account whether the information likely to be obtained would affect the patient's care. There are 2 general indications for performing a liver biopsy in patients with suspected NAFLD:

1. Confirming the diagnosis and staging the disease. Establishing the diagnosis, activity grade (degree of inflammation and cellular injury), and stage of fibrosis of NAFLD requires a liver biopsy. Given the high prevalence in the population, the invasive nature of liver biopsy, and the paucity of effective therapies, however, there is often an understandable reluctance to perform liver biopsy for the sole purpose of confirming the diagnosis. In most patients, therefore, the diagnosis of suspected NAFLD is based on clinical and laboratory data, and imaging studies with appropriate exclusion of other liver conditions.
2. Determining prognosis based on the severity of liver injury and fibrosis. Liver biopsy is the only investigation that can reliably distinguish between simple steatosis and NASH, as well as stage the extent of fibrosis. The prognosis of NAFLD depends on the severity of liver injury and fibrosis. While most studies suggest that there is no increased mortality associated with simple steatosis, mortality in patients with NASH, particularly those with advanced fibrosis and cirrhosis, is increased as compared to the general population of same age and gender. For instance, the prevalence of cirrhosis and liver-related mortality within the first 15 years of diagnosis is less than 1% (0.7% and 0.9% respectively) in patients with bland steatosis, but this increases to 11% and 7%, respectively, in patients with NASH.[9] The highest liver-related morbidity and mortality are undoubtedly among those patients with advanced (stage 3 or 4) fibrosis.[10–12] Additionally, the identification of early cirrhosis or advanced (bridging) fibrosis may alter management, as such patients should undergo upper endoscopies to screen for gastroesophageal varices and periodic liver ultrasound imaging to screen for hepatocellular carcinoma.[12]

Hence, in the absence of clinical and radiologic features of cirrhosis, liver biopsy remains the only way to reliably assess prognosis.

Over the last decade, several simple laboratory tests (in isolation or in combination), serum markers of fibrogenesis, and imaging studies (ultrasound, computed tomography [CT] and magnetic resonance imaging [MRI]) have been evaluated as a substitute for liver biopsy in NAFLD and had showed varying degrees of accuracy when compared to liver biopsy. There remains a high degree of interest in accurately diagnosing, grading, and staging this disease noninvasively.

LIMITATIONS OF LIVER BIOPSY

The potential drawbacks of liver biopsy are well documented. These include sampling error, problems with inadequate biopsy size, variability in pathologist interpretation,