MAYO CLINIC

REVIEW

Recommendations for Diagnosis, Referral for Liver Biopsy, and Treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the primary cause of chronic liver disease in the United States, afflicting an estimated 80 to 100 million Americans. Nonalcoholic fatty liver disease is a spectrum of liver diseases composed of nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH). Although nonalcoholic fatty liver has a negligible risk of progression, patients with NASH often develop cirrhosis or hepatocellular carcinoma. Although liver biopsy is required to diagnose NASH, only patients with a high risk of NASH or advanced fibrosis require this evaluation. Despite the high prevalence of NAFLD, well-defined screening recommendations are currently lacking. In this review, suggestions for screening, diagnosis, and initial work-up of NAFLD are given on the basis of established guidelines and recent publications. Proposed drug treatments of NASH are also discussed, highlighting the study outcomes, as well as proposed uses and limitations of these drugs. The literature was searched in PubMed using search terms *nonalcoholic fatty liver disease* and *nonalcoholic steatohepatitis*, with filters of "English language." A date range of January 1, 2000, to May 1, 2015, was used for the search. The bibliographies of key references were also searched manually, and seminal publications before the year 2000 were included.

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Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States, and its prevalence and clinical importance is increasing worldwide.[1,2] Recent studies estimate that between 30% and 40% of the population in the United States (80 to 100 million Americans) is affected by NAFLD.[3-6] The number of people at risk for NAFLD is even greater, given the increasing prevalence of obesity, diabetes, and metabolic syndrome.[6] Nonalcoholic steatohepatitis (NASH) is a frequently progressive subset of NAFLD that can be complicated by cardiovascular disease, cirrhosis, and hepatocellular carcinoma (HCC).[7,8] Although there are no Food and Drug Administration–approved medications for NASH, there are several medications that have shown benefits in clinical trials. The uses and limitations of these medications will be discussed in detail (Table 1). Prompt diagnosis, timely referrals, and effective treatments are necessary to improve the long-term outcomes of patients with NAFLD and NASH in the setting of primary care and general gastroenterology practices. This review will focus on these important aspects of patient care.

The content of this review is based on a search of the literature performed in PubMed using the following search terms: *nonalcoholic fatty liver disease* and *nonalcoholic steatohepatitis*. Studies published in the non-English scientific literature were excluded. A date range of January 1, 2000, to May 1, 2015, was used for the search. The bibliographies of key references were also searched manually, and seminal publications before the year 2000 were included.

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HISTOLOGY, EPIDEMIOLOGY, AND DISEASE COURSE

Nonalcoholic fatty liver disease is characterized by hepatic steatosis, without a history of excessive alcohol use, in the absence of other known liver diseases.[1] Nonalcoholic fatty liver disease is categorized into 2 subtypes: nonalcoholic fatty liver (NAFL), which

ARTICLE HIGHLIGHTS

- Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases composed of nonalcoholic fatty liver, which has a negligible risk of progression, and nonalcoholic steatohepatitis (NASH), which has a higher risk of liver disease progression. Nonalcoholic steatohepatitis is histologic diagnosis based on liver biopsy findings of steatosis, ballooning, and lobular inflammation; this disease is associated with an increased risk of cardiovascular death, cirrhosis, end-stage liver disease, and hepatocellular carcinoma.
- Patients with suspected or known NAFLD and a high risk of NASH or advanced fibrosis should be referred for consideration of liver biopsy.
- Lifestyle modifications, including weight loss and exercise, form the cornerstone of NAFLD treatment and should be strongly encouraged. Vitamin E and pioglitazone have been shown to benefit select patients with biopsy-proven NASH.
- Statins and metformin therapy are not indicated for the treatment of NASH, but are safe and effective in patients with NASH with other clinical indications for their use, such as dyslipidemia and diabetes.

is usually nonprogressive, and NASH, which is often progressive and can lead to cirrhosis and HCC.[3] Nonalcoholic fatty liver and NASH have traditionally been considered 2 separate clinical entities, rather than 2 points on a disease continuum.[9] Recent studies evaluating sequential liver biopsies are challenging this notion.[10-12] A systematic review and meta-analysis of paired biopsy studies found that both patients with NAFL and NASH have the potential to develop progressive liver disease.[13] The fibrosis progression rate from stage 0 to stage 1 for NAFL vs NASH is 14 years vs 7 years, providing suggestive evidence that NAFL, NASH, and fibrosis progression are a continuum rather than separate diagnoses.[13] Patients with NAFL and mild lobular inflammation, without ballooning, had an increased risk of disease progression as compared with those without inflammation.[13] Another retrospective study evaluated serial liver biopsies in 108 patients and found no significant difference in the proportion of fibrosis progression between patients with NAFL and those with NASH at index biopsy (37% vs 43%; P=.65).[12] Similarly, a recent study analyzing paired liver biopsies over time found that even patients with bland steatosis can progress to NASH, especially in the setting of metabolic risk factors.[14]

Establishing an accurate diagnosis of NASH is of major clinical importance. A histologic diagnosis of NASH is associated with cardiovascular disease[15] and more rapid progression of liver disease.[13] To accurately distinguish NASH from NAFL requires liver biopsy. Nonalcoholic fatty liver is defined as bland steatosis with minimal or no inflammation, whereas NASH is characterized by macrovesicular steatosis, ballooning, and mixed lobular inflammation with or without zone 3 perisinusoidal fibrosis[16] (Figure 1). Steatosis and ballooning in adults with NASH are most commonly zone 3 predominant or panacinar.[17,18] When advanced fibrosis develops, the zonal distribution of steatosis and ballooning is often lost.[17,18] Acidophil bodies (compact eosinophilic cells representing apoptotic hepatocytes) and Mallory-Denk bodies (ropey intracytoplasmic inclusions composed of damaged intermediate filaments) are also frequently seen on biopsies from patients with NASH but are not required for the diagnosis.[16]

In the Western world, NAFLD is most commonly associated with obesity, metabolic syndrome, and diabetes.[19] As with other metabolic conditions, NAFLD appears to have a strong genetic component. Both family history of diabetes and Hispanic ethnicity have been identified as risk factors.[19] The first genome-wide association study of NAFLD identified that the variant I148M (rs738409) located in human patatin-like phospholipase domain–containing protein 3 gene (*PNPLA3*) was associated with increased hepatic fat content and hepatic inflammation.[20] This allele was found at a higher frequency in Hispanic patients, providing one possible reason for increased susceptibility in this population. Metabolic syndrome, diabetes, and advanced age have all been shown to increase the risk of liver disease progression in patients with NAFLD.[19,21,22]

It is estimated that NASH occurs in 20% of patients with NAFLD (3%-12% of the US population).[5,6] Approximately 30% to 40% of patients with NASH will develop