Practice Guidelines

Nonalcoholic Fatty Liver Disease: Diagnosis and Management Guidelines From the AACE

Key Points for Practice

- NAFLD and NASH are common in patients with type 2 diabetes and obesity.
- If testing for NAFLD, start with the fibrosis-4 index, which uses platelet and transaminase measurements. Evaluate intermediate- or higher-risk patients with transient elastography or an enhanced liver fibrosis laboratory panel.
- Weight loss is key to managing NAFLD and NASH; lifestyle interventions, glucagon-like peptide-1 agonists, and bariatric surgery all improve liver disease.

From the *AFP* Editors

Nonalcoholic fatty liver disease (NAFLD) affects one-fourth of the global population and is the most common cause of chronic liver disease. Up to 1 in 7 people with NAFLD have a more aggressive form called nonalcoholic steatohepatitis (NASH), which can progress to advanced liver fibrosis, cirrhosis, or liver cancer. Fewer than 1 in 20 people with NAFLD is aware that they have the disease. The American Association of Clinical Endocrinology (AACE) published guidelines for diagnosis and management of NAFLD, cosponsored by the American Association for the Study of Liver Diseases.

Epidemiology

Because NAFLD is defined by hepatic steatosis in more than 5% of hepatocytes in a biopsy sample, the prevalence must be estimated. It is important to diagnosis the lack of significant recent or ongoing alcohol consumption or other known causes of liver disease. Significant alcohol use is defined as more than 21 standard drinks per week for men and 14 drinks per week for women.

Among patients with type 2 diabetes mellitus, about 70% have NAFLD, up to 40% have NASH, and 15% have clinically significant fibrosis. Up to 30% of people with obesity have NASH. NAFLD affects just less than one-fourth of patients with type 1 diabetes. Although hypothyroidism seems to increase the risk of NAFLD, treatment with levothyroxine increases the NAFLD risk even more. Growth hormone deficiency is also associated with NAFLD, although the effects of treatment are uncertain.

Most of the serious sequelae from NAFLD come from those with NASH. Approximately 20% of

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This series is coordinated by Michael J. Arnold, MD, contributing editor.

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CME This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 458.

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G-TRUST GUIDELINE SCORECARD

Score	Criteria
No	Focus on patient-oriented outcomes (exclusively disease-oriented outcomes)
Yes	Clear and actionable recommendations
Yes	Relevant patient populations and conditions
Yes	Based on systematic review
Yes	Evidence graded by quality
Yes	Separate evidence review or analyst in guideline team
No	Chair and majority free of conflicts of interest (one cochair with significant conflicts)
No	Development group includes most relevant specialties, patients, and payers
	Overall – not useful

Note: See related editorial, Where Clinical Guidelines Go Wrong, at https://www.aafp.org/afp/gtrust.html.

G-TRUST = guideline trustworthiness, relevance, and utility scoring tool.

patients with NASH will develop significant liver disease. NASH is among the top causes of hepatocellular carcinoma.

Diagnosis

HIGH-RISK PATIENTS

Because of the high prevalence of NAFLD in patients with type 2 diabetes and obesity, screening these patients should be considered. Similarly, people with metabolic syndrome, insulin resistance, and diabetes are at increased risk of fibrosis and mortality and can be considered for screening. Liver biopsy at the time of bariatric surgery should be considered because nearly 1 in 12 patients will have significant fibrosis, and up to 1 in 25 patients will have cirrhosis. Patients with persistently elevated transaminase levels are at high risk of NAFLD and developing hepatic fibrosis.

TESTING FOR NAFLD

The first step to testing for NAFLD is to estimate fibrosis through the fibrosis-4 index (https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis), the most highly validated initial test, which uses platelet and transaminase measurements. The fibrosis-4 index has a high negative predictive value but low positive predictive value. Other suggested fibrosis indexes appear to further overestimate fibrosis.

Alanine transaminase levels alone cannot rule out NAFLD because one-half of patients with NAFLD and type 2 diabetes have levels in the normal range. Liver ultrasonography is not effective for screening because of low sensitivity for mild to moderate steatosis.

For an intermediate- or high-risk fibrosis-4 index, liver stiffness should be measured using transient elastography. This testing can rule out fibrosis with negative predictive values between 91% and 99%, depending on the specification used. Magnetic resonance elastography is also accurate, but it is less widely available.

If transient elastography is not available, an enhanced liver fibrosis laboratory panel can be used to estimate the rate of liver extracellular matrix metabolism. Use of the fibrosis-4 index and enhanced liver fibrosis testing reduces unnecessary hepatology referrals and increases identification of patients with advanced fibrosis.

Management

Management of NAFLD is primarily focused on lifestyle changes. A few medications have disease-oriented evidence of benefit but have not been studied for their effect on patient outcomes.

LIFESTYLE

Weight loss proportionally reduces hepatic steatosis. In a study of a 52-week intensive lifestyle program in patients with NASH, 90% of patients who lost more than 10% of initial body weight had resolution of NASH, and 45% had regression of fibrosis. The Mediterranean and calorie-restricted Dietary Approaches to Stop Hypertension (DASH) diets appear beneficial. Exercise appears consistently beneficial, especially when paired with dietary changes.

MEDICATIONS

Pioglitazone increases resolution of NASH, especially in patients with advanced fibrosis. Pioglitazone commonly causes weight gain and heart failure and carries a small risk of bladder cancer.

Glucagon-like peptide-1 agonists increase the resolution of steatohepatitis. Whether this improvement is due to the medication or the weight loss is unknown. Sodium-glucose cotransporter-2 inhibitors improve hepatic steatosis on imaging, but no biopsy evidence is available. Metformin does not appear to improve steatohepatitis or fibrosis.

SURGERY

Bariatric surgery leads to resolution of NASH in two-thirds of patients and fibrosis improvement in 40%. Yet, nearly 1 in 8 patients will have worsening of fibrosis after bariatric surgery. One study, with five-year follow-up after bariatric surgery, demonstrated resolution of NASH in 90% of patients and improvement in fibrosis in 70%. If cirrhosis and stage 3 fibrosis are present, the surgical risks may outweigh the benefits. Endoscopic bariatric procedures lack evidence for patients with NASH.

Children

NAFLD affects 1 in 13 children overall, 1 in 3 children with obesity, and one-half of children with prediabetes or type 2 diabetes. Adolescents with polycystic ovary syndrome also have increased risk of NAFLD. Children with polycystic ovary syndrome, obesity, prediabetes, or type 2 diabetes should be screened for NAFLD.

Little evidence exists to guide treatment of NAFLD in children. Lifestyle advice has been shown to improve steatohepatitis and fibrosis in some children, whereas others worsened.

Metformin and vitamin E do not improve steatohepatitis in children with NASH. Glucagon-like peptide-1 agonists are recommended based on evidence of reducing obesity.

Editor's Note: Many family physicians struggle with how and whether to diagnose and manage NAFLD in our patients. Although the AACE argument of high prevalence and impact is compelling, the lack of patient-oriented evidence that leads this guideline to fail the G-TRUST scorecard highlights the uncertainty of what to do. Additionally, few treatment options for NAFLD are available that do not also apply to care of obesity and diabetes. Do we need another reason to encourage lifestyle changes, and will this diagnosis be the motivating factor? The benefit of glucagon-like peptide-1 agonists and sodium-glucose cotransporter-2 inhibitors may simply be tied to the weight loss they cause.

The evidence for pioglitazone is more complicated. With only disease-oriented evidence from five trials including just more than 500 patients, the authors of the meta-analysis referenced by the guideline note that trials were too small to allow assessment for adverse events.[1] With the known risks of weight gain, edema, and bladder cancer, I find myself hesitant to go back to the early 2000s and prescribe this medication again.

We are left with known sequelae of obesity and insulin resistance that are challenging to treat and underline only the importance of obesity interventions that we all currently struggle to implement. Whether screening and diagnosis are worthwhile remains an open question, similar to the ongoing debate surrounding prediabetes.—Michael J. Arnold, MD, Contributing Editor

Reference

1. Musso G, Cassader M, Paschetta E, et al. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis [published correction appears in *JAMA Intern Med.* 2017;177(5):747]. *JAMA Intern Med.* 2017;177(5):633-640.

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Answers to This Issue's CME Quiz

Q1. B	Q6. A	Q11. B	Q16. B
Q2. D	Q7. C	Q12. C	Q17. B
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