JAMA Clinical Guidelines Synopsis

Diagnosis and Management of Nonalcoholic Fatty Liver Disease

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GUIDELINE TITLE American Association of Clinical Endocrinology (AACE) Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

RELEASE DATE May 2022

DEVELOPER AND FUNDING SOURCE AACE and American Association for the Study of Liver Diseases (AASLD)

TARGET POPULATION Patients at risk of nonalcohol fatty liver disease (NAFLD)

MAJOR RECOMMENDATIONS

- Screen persons with (1) prediabetes or type 2 diabetes, (2) obesity or ≥2 cardiometabolic risk factors, and/or (3) abnormal serum aminotransaminases or hepatic steatosis on imaging for NAFLD and advanced fibrosis (grade B; intermediate/high strength of evidence [SOE]).
- Use noninvasive liver fibrosis clinical prediction tools like the Fibrosis-4 Index (FIB-4) to initially assess risk of NAFLD and liver fibrosis (grade B; intermediate SOE).
- Evaluate risk of fibrosis in persons with NAFLD with vibration-controlled transient elastography (VCTE) or enhanced liver fibrosis (ELF) score (grade B; intermediate SOE).
- Refer patients to specialists when there are persistently elevated aminotransferases or hepatic steatosis on imaging with indeterminate or high-risk noninvasive results (FIB-4 >1.3, elevated liver stiffness measurement, or positive ELF results) (grade B; intermediate SOE).
- Treat cardiometabolic disease in persons with NAFLD (grade A; high/intermediate SOE).
- Recommend dietary modification and physical activity (150 min/wk) in persons with excess adiposity and NAFLD (grade A; intermediate SOE).
- Initiate pioglitazone and/or glucagon-like peptide 1 receptor agonists (GLP1RAs), especially in type 2 diabetes and biopsy-proven nonalcoholic steatohepatitis (NASH), and strongly consider adjunctive obesity pharmacotherapy with lifestyle modifications for individuals with obesity, diabetes, and NAFLD (grade A; high/intermediate SOE).
- Consider bariatric surgery to treat NAFLD in persons with a body mass index >35 (grade B; intermediate/weak SOE).

Summary of the Clinical Problem

NAFLD is characterized by hepatic steatosis associated with metabolic abnormalities such as insulin resistance, dyslipidemia, obesity, and hypertension. Prevalence of NAFLD in US adults approaches 40%, with high-risk fibrosis more than doubling between 2000 and 2016 (National Health and Nutrition Examination Survey).[1] Less than 5% of patients with NAFLD are aware of their condition, and 12% to 14% also have NASH, which can progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma. Diagnostic screening and initial treatment for NAFLD can often be carried out in primary care settings.[2]

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Characteristics of the Guideline Source

The guideline was developed by the AACE and AASLD and funded by the AACE. The development panel included AACE member or AASLD representative endocrinologists and hepatologists. A literature review identified 385 supporting studies published January 1, 2010, to November 15, 2021. Through consensus, grading was assigned to each recommendation. Panel members disclosed potential conflicts of interest (**Table**).

Evidence Base

Diagnosis of NAFLD is based on (1) presence of hepatic steatosis in more than 5% of hepatocytes, (2) absence of significant alcohol consumption (>21 [men] or >14 [women] drinks/wk), and (3) excluding presence of other liver diseases. Early intervention can halt or reverse disease progression. High-risk conditions that warrant NAFLD screening include (1) prediabetes or type 2 diabetes; (2) obesity or 2 or more cardiometabolic risk factors for metabolic syndrome such as elevated triglycerides (≥150 mg/dL) or waist circumference (>40 in [men] or >35 in [women]); and (3) either hepatic steatosis on imaging or persistent high (>30 U/L) serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT). NAFLD prevalence in persons with type 2 diabetes may be as high as 70%, of whom 15% have moderate or severe fibrosis.[2]

Noninvasive clinical tools that measure liver fibrosis such as the FIB-4 should be used to assess for fibrosis more severe than minimal scarring. The FIB-4 includes age, platelet count, AST, and ALT, which predicts risk of hepatic cirrhosis and other liver-related adverse events in adults (area under the curve, 0.71-0.89).[3] Even with clinically significant fibrosis, the majority of patients with NAFLD in

Table. Guideline Rating[a]

Standard	Rating
Establish transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Fair
Clinical practice guideline-systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Fair
External review	Poor
Updating	Fair
Implementation issues	Fair

[a] Cifu AS, Davis AM, Livingston EH. Introducing JAMA Clinical Guidelines Synopsis. *JAMA*. 2014;312(12):1208-1209. doi:10.1001/jama.2014.12712

primary care or endocrine clinic settings have AST and ALT of less than 40 U/L.[2] FIB-4 categorizes patients into low risk (FIB-4 <1.3), indeterminate risk (FIB-4 1.3-2.67), or high risk (FIB-4 >2.67). Persons with indeterminate risk can have further staging with liver stiffness measurement by VCTE or with the ELF score, a proprietary fibrosis biomarker test. This 2-step approach (FIB-4, then liver stiffness measurement by VCTE or ELF score) can reduce low-risk referrals to specialists.[2,4] Persons with persistently elevated ALT or AST or hepatic steatosis on imaging with indeterminate or high risk (FIB-4 >1.3, liver stiffness measurement by elastography >8 kPa, or ELF score >7.7) should be referred to a hepatologist.[2]

Patients with NAFLD should receive treatment for obesity, insulin resistance/prediabetes, dyslipidemia, and hypertension. Cardiovascular disease is the leading cause of death associated with NAFLD.[2,5] Dietary modifications and adherence to physical activity are first-line therapy in people with excess adiposity and NAFLD to support sustained weight loss. Weight loss achieved through caloric deficit and 150 minutes of weekly physical activity can reduce hepatic steatosis, albeit less consistently for those with fibrosis. A review[6] found that 5% weight loss regardless of method (lifestyle modifications, pharmacotherapy, or surgery) was correlated with a 30% relative reduction in intrahepatic triglyceride content (r = 0.71; P < .001). The AACE recommends a weight loss goal of at least 5%, and preferably 10%, as more weight loss is associated with decreased hepatic steatosis, resolution of NASH, and reduction in hepatic fibrosis and improved cardiometabolic parameters.

Pharmacotherapy for obesity should be considered in patients with obesity, diabetes, and NAFLD. GLP1RAs are recommended for these patients as they are associated with decreased hepatic steatosis, although a statistically significant reduction in fibrosis has not been reported. In a phase 2 randomized clinical trial (RCT) of patients with biopsy-proven NASH, 59% who received semaglutide 0.4 mg/d injections had resolution of NASH and no fibrosis worsening vs 17% with placebo (odds ratio [OR], 6.87; 95% CI, 2.60-17.63; P < .001).[7] Trials of semaglutide and tirzepatide (a glucose-dependent insulinotropic polypeptide receptor agonist [GIPRA]/GLP1RA) are ongoing. High cost, lack of insurance, or inadequate insurance coverage may limit access to weight management medications. Pioglitazone (a thiazolidinedione) may be considered and costs less than GLP1RAs and GIPRAs/GLP1RAs. In a meta-analysis of 5 RCTs (392 individuals) with biopsy-proven NASH, pioglitazone vs placebo or vitamin E was associated with resolution of NASH (OR, 3.65; 95% CI, 2.32-5.74; P < .001) and improved hepatic fibrosis at any stage (OR, 1.77; 95% CI, 1.15-2.72; P = .009), but especially in advanced fibrosis (OR, 10.17; 95% CI, 2.83-36.54; P < .001), even in adults without type 2 diabetes.[8] However, pioglitazone was associated with a mean 2.51% weight gain (95% CI, 0.36%-4.66%).[8] Pioglitazone is contraindicated in patients with New York Heart Association class III or IV heart failure. Bariatric surgery is a potential treatment option for patients with NAFLD, especially those with body mass index [BMI] greater than 35 (with consideration for people of Asian race with BMI >32.5) and type 2 diabetes, given its established role in substantial weight loss.

Discussion

Primary care clinicians can diagnose and initiate treatment of NAFLD. Many effective pharmacotherapy options do not require initiation and monitoring by specialists. These guidelines define triggers for referrals to hepatologists and bariatric surgeons. The AASLD published a new guidance document in March 2023 on assessment and management of NAFLD with a focus on advances in noninvasive risk stratification and therapeutics.[9] The recommendations highlighted above are in agreement with those recommendations.

Areas in Need of Future Study or Ongoing Research

Several large international liver disease societies recommended changing the nosology of fatty liver disease to steatotic liver disease (SLD), with subcategories of metabolic dysfunction–associated steatotic liver disease (MASLD), alcohol liver disease (ALD), and the combination of MASLD and ALD as "MetALD."[10] The impact of this shift will need to be evaluated in subsequent studies and reflected in updated guidelines. Upcoming data from larger RCTs of GLP1RAs, GIPRAs/GLP1RAs, and sodium-glucose cotransporter 2 inhibitors should help clarify their direct effects on NASH. Studies underway have the potential to improve quantification of hepatic fibrosis and evaluate treatment response, as well as approaches that apply genetic disease modifiers and identification of disease phenotypes, to improve tailoring of therapies for patients with NAFLD.

ARTICLE INFORMATION

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