JAMA Clinical Guidelines Synopsis

Diagnosis and Management of Nonalcoholic Fatty Liver Disease

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GUIDELINE TITLE Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases

DEVELOPER American Association for the Study of Liver Diseases (AASLD)

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PRIOR VERSION June 2012

FUNDING SOURCE AASLD

TARGET POPULATION Individuals with nonalcoholic fatty liver disease (NAFLD)

MAJOR RECOMMENDATIONS

- Patients with incidental hepatic steatosis detected on imaging who lack any liver-related symptoms or signs and have normal liver biochemistries should be assessed for metabolic risk factors (eg, obesity, diabetes mellitus, dyslipidemia) and other causes of hepatic steatosis, including alcohol consumption (>14 drinks per week for women; >21 drinks per week for men) and medications.
- Routine screening for NAFLD in high-risk groups is not advised because of uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge about long-term benefits and cost-effectiveness of screening.
- The FIB-4 (age, aspartate aminotransferase, alanine aminotransferase, platelets) and NAFLD Fibrosis Score (NFS, which adds body mass index and albumin) are clinically useful tools to predict bridging fibrosis.
- Vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE) can noninvasively assess for advanced fibrosis.
- Weight loss generally reduces hepatic steatosis, either by hypocaloric diet alone or in conjunction with increased physical activity.
- Pharmacologic treatments should be limited to patients with biopsy-proven nonalcoholic steatohepatitis (NASH) and advanced fibrosis.
- Statins can be used to treat dyslipidemia in patients with NAFLD, NASH, and compensated NASH cirrhosis.

Summary of the Clinical Problem

Nonalcoholic fatty liver disease affects about 25% of the adult population globally and is strongly associated with metabolic syndrome, affecting most patients who have dyslipidemia, obesity, or type 2 diabetes .[1] About 2% to 7% of those with NAFLD have evidence of NASH on liver biopsy with hepatic inflammation and injury.[2] Long-standing NAFLD and NASH can result in cirrhosis and its complications, including hepatocellular carcinoma. Currently, NASH ranks as the second most common reason for liver transplant in the United States and will likely surpass hepatitis C in the coming years as the most common. A diagnosis of NAFLD requires evidence of hepatic steatosis (on imaging or histology) in the absence of secondary causes of steatosis or other liver disease, such as excessive alcohol intake, hepatitis C, Wilson disease, and hepatotoxic medications. Methods to noninvasively assess for advanced fibrosis (bridging fibrosis or cirrhosis) are evolving and can help target which patients should receive a liver biopsy and, potentially, pharmacologic therapy.

Characteristics of the Guideline Source

This practice guidance is an update of the 2012 practice guideline and was commissioned by the AASLD and developed by a panel of experts (**Table**). Updates to the previous guidelines and guidance statements were made based on review of published literature in MEDLINE up to August 2016 and author expertise. Statements were evidence based if possible, but if insufficient evidence was available, statements were based on consensus opinion of the authors.

Evidence Base

The NFS was shown in a large meta-analysis to have a receiver operating curve of 0.85 in predicting advanced fibrosis.[1] Additionally, the NFS and FIB-4 perform as well as MRE in predicting advanced fibrosis in patients with biopsy-proven NAFLD.[3] Diet and exercise remain the mainstay of therapy for NAFLD. The guideline cites evidence that weight loss of 5% to 7% was associated with the stabilization or improvement of liver fibrosis on biopsy, and weight loss of 10% was associated with improvement in all histologic features of NASH. A multicenter trial of patients without diabetes who had NASH[4] randomized 247 patients to pioglitazone (30 mg/d), vitamin E (800 IU/d), or placebo for 24 months. The primary end point was improvement in hepatocellular ballooning and either lobular inflammation score or steatosis score, achieved in 19% in the placebo group vs 34% in the pioglitazone group (P = .04) and 43%

Table. Guideline Rating

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

in the vitamin E group ($P = .001$). A second trial randomized 101 patients with diabetes or prediabetes to diet plus either pioglitazone or placebo[5] and found resolution of NASH in 51% of those taking pioglitazone vs 19% taking placebo ($P < .001$). The authors suggested monitoring to identify patients at risk of congestive heart failure or long-term effects on bone metabolism.

Benefits and Harms

This practice guidance provides a structured approach to determining patients at risk of NAFLD, with a focus on identifying those with advanced fibrosis. Both VCTE and MRE can help identify advanced fibrosis but may not be widely available owing to cost and variable insurance coverage. Lifestyle changes remain the cornerstone of therapy. A systematic review of 24 studies assessing liver outcomes (including 8 by magnetic resonance imaging, 5 by ultrasound, and 3 by biopsy) supported reduction of daily caloric intake in combination with 30 to 60 minutes of exercise 3 to 5 days per week.[6] Consistent and sustainable results likely require a multidisciplinary approach involving specialty clinics.[6] Meta-analyses of vitamin E supplementation at 400 to 800 IU/d have had opposite conclusions regarding an association with increased all-cause mortality, and 1 randomized trial unexpectedly associated vitamin E with a modest increase in prostate cancer.[1] Pioglitazone is associated with weight gain, with inconsistent evidence linking it to heart failure, bladder cancer, and bone loss in women.[1] The guideline thus recommends that both of these therapies should be directed only to patients with biopsy-proven NASH, with risks and benefits carefully discussed and the decision individualized to patients. The guidance suggests considering biopsy particularly when competing etiologies of hepatic steatosis and presence and/or severity of coexisting chronic liver diseases cannot be determined without its use.

Discussion

This guidance may help standardize evaluation and management of patients with NAFLD. The AASLD practice guidance is similar to the UK National Institute for Health and Care Excellence (NICE) guidelines for NAFLD. Both stress the prevalence of metabolic syndrome and type 2 diabetes in NAFLD, note its contribution to cardiovascular mortality, and encourage statin use in patients with NAFLD, except in decompensated cirrhosis. While both stress the central role of lifestyle modifications, the potential benefits of a Mediterranean diet perhaps deserve greater support.[7] Medication guidance also varies. The AASLD advises pioglitazone in patients with biopsy-proven NASH with and without type 2 diabetes, and vitamin E in only patients without diabetes and with biopsy-proven NASH without cirrhosis. In contrast, NICE suggests pioglitazone or vitamin E for all patients with advanced liver fibrosis.

The 2016 European clinical practice guidelines suggest screening patients older than 50 years with type 2 diabetes or metabolic syndrome for NAFLD by liver tests and/or ultrasound, and the NICE guidelines suggest screening in younger adults. In contrast, the AASLD guidelines recommend against population screening, noting poor evidence for longer-term benefits and cost-effectiveness.

Areas in Need of Future Study or Ongoing Research

The value of screening those at high risk of development of NAFLD remains to be established, given limitations and uncertain cost-effectiveness of current diagnostic testing and treatment options. Lifestyle interventions to reduce obesity and diabetes remain the mainstay of treatment, but additional practical interventions are required at the patient, clinic, and societal level. The potential of bariatric surgery is noted in the guideline, but its role remains to be established. The value of coffee intake merits additional exploration,[8] as does the benefit of various pharmacologic therapies, including clinical trials of glucagon-like peptide-1 agonists,[9] obeticholic acid, and elfibrinaor.[10] More accurate biomarkers to identify steatohepatitis and advanced fibrosis would be welcome. For example, NICE guidelines recommend the enhanced liver fibrosis panel, consisting of plasma levels of 3 matrix turnover proteins, but this is not yet approved in the United States.

Related guidelines and other resources

FIB-4 score
http://gihep.com/calculators/hepatology/fibrosis-4-score/

NAFLD Fibrosis Score
http://gihep.com/calculators/hepatology/nafld-fibrosis-score/

NICE NAFLD guidelines (2016)
https://www.nice.org.uk/guidance/ng49

European NAFLD consensus guidelines (2016)
https://link.springer.com/article/10.1007%2Fs00125-016-3902-y

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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