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AMERICAN GASTROENTEROLOGICAL ASSOCIATION

American Gastroenterological Association Medical Position Statement: Nonalcoholic Fatty Liver Disease

This document presents the official recommendations of the American Gastroenterological Association (AGA) and the American Association for the Study of Liver Diseases (AASLD) on Nonalcoholic Fatty Liver Disease. It was approved by the Clinical Practice Committee on March 3, 2002, and by the AGA Governing Board on May 19, 2002. It was approved by the AASLD Governing Board and AASLD Practice Guidelines Committee on May 24, 2002.

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of disorders characterized by predominantly macrovesicular hepatic steatosis that occur in individuals even in the absence of consumption of alcohol in amounts considered harmful to the liver. NAFLD is being increasingly recognized as a major cause of liver-related morbidity and mortality. The likelihood of having NAFLD is directly proportional to body weight. Given the increasing prevalence of obesity in North America, NAFLD is an important public health problem. These considerations have led to the development of the technical review and practice guidelines statement, which are sponsored by the American Gastroenterological Association (AGA) and the American Association for the Study of Liver Diseases (AASLD).

These guidelines, intended for use by physicians, suggest preferable approaches to the diagnostic and therapeutic aspects of care. The guidelines are recommendations intended to assist the physician in making patient care decisions.[1] They are intended to be flexible, in contrast to "standards of care," which are inflexible policies to be followed in almost every case. Thus, although the recommendation should be followed in most cases, the decision to do so is up to the physician based on the circumstances of the individual case. Specific recommendations are based on relevant and published information. In circumstances in which the literature does not provide data on which to base clinical decisions, the clinical alternatives are outlined. In an attempt to standardize recommendations, the Practice Guidelines Committees of the AGA and AASLD have developed categories based on the quality of the data supporting specific recommendations (Tables 1–3). These are noted at the end of each guideline.

When Should the Presence of NAFLD Be Suspected?

The presence of underlying NAFLD should be considered in those who have risk factors for this condition. Such risk factors include obesity, diabetes, hypertriglyceridemia, severe weight loss (especially in those who were obese initially), and specific syndromes associated with insulin resistance (e.g., lipoatrophic diabetes) (Table 4). NAFLD should also be considered in the differential diagnosis of elevated serum aminotransferase levels in individuals who are receiving drugs known to be associated with NAFLD. Finally, the presence of NAFLD should also be considered in those with persistent elevation of serum alanine aminotransferase levels for which another cause cannot be found.

Recommendation category: AGA: III and IV; AASLD: B, III

Evaluation of a Patient With Suspected NAFLD

Clinical and Laboratory Evaluation

The initial clinical and laboratory assessment of a patient with suspected NAFLD should be determined by the specific clinical circumstances in an individual case (Figure 1). Serum aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels (biochemical markers of liver injury and cholestasis) and liver functions (serum bilirubin, albumin, and prothrombin time) should be measured (step 1). The presence of alternative or coexisting clinical conditions (e.g., hepatitis C) should be assessed using the relevant laboratory test (step 2). An attempt to estimate the extent of underlying alcohol consumption should be made (step 3). This usually involves a detailed clinical evaluation, including interview of family members in some cases, and assessment of the aspartate aminotransferase/alanine aminotransferase ratio. In the absence of cirrhosis, when the aspartate aminotransferase/alanine aminotransferase ratio exceeds 2, the diagnosis of alcoholic liver disease may be made with greater confidence.

Recommendation category: AGA: III and IV; AASLD: B, III

Table 1. Sample Coding System for Hierarchy of Evidence Used by the AGA

Level of evidence	
I	Well-designed randomized controlled trials
II-1a	Well-designed controlled trials with pseudo-randomization
II-1b	Well-designed controlled trials with no randomization
II-2a	Well-designed cohort (prospective) study with concurrent controls
II-2b	Well-designed cohort (prospective) study with historical controls
II-2c	Well-designed cohort (retrospective) study with concurrent controls
II-3	Well-designed case-control (retrospective) study
III	Large differences from comparisons between times and/or places with and without intervention (in some instances, these may be equivalent to level II or I)
IV	Opinions of respected authorities based on clinical experience, descriptive studies, and reports of expert panels

Adapted from CRD report #4.[2]

Confirmation of Fatty Liver Disease

Once ongoing alcohol use (>20–30 g/day) and other common causes of liver disease are excluded by clinical and laboratory evaluation, the liver is usually imaged by sonography, computerized tomography scan, or magnetic resonance imaging (step 4). These modalities can be used to determine the presence of biliary tract disease and focal liver disease, which may be responsible for elevation of liver enzyme levels. However, they do not distinguish between fatty liver, steatohepatitis, and steatohepatitis with fibrosis and therefore cannot be used to make these distinctions. Although sonography is slightly more sensitive, computerized tomography scan is more specific but more expensive. Sufficient data on the comparative assessment of these tests, including their cost and predictive values, on which to base a recommendation are lacking. Hence, a recommendation about the use of one modality versus another cannot be made at this time. It is, however, common practice to use either sonography or computerized tomography scan.

Table 2. Categories Reflecting the Evidence to Support the Use of a Guideline Recommendation by the AASLD

Category	Definition
A	Survival benefit
B	Improved diagnosis
C	Improvement in quality of life
D	Relevant pathophysiologic parameters improved
E	Impacts cost of health care

Adapted and modified from Gross et al.[3]

Table 3. Quality of Evidence on Which Recommendation Is Based as Categorized by the AASLD

Grade	Definition
I	Evidence from multiple well-designed randomized controlled trials, each involving a number of participants to be of sufficient statistical power
II	Evidence from at least one large well-designed clinical trial with or without randomization from cohort or case-control analytic studies or well-designed meta-analyses
III	Evidence based on clinical experience, descriptive studies, or reports of expert committees
IV	Not rated

Adapted and modified from Gross et al.[3]

Recommendation category: AGA: II, III, IV; AASLD: B, II, III

The diagnosis of steatohepatitis, as opposed to fatty liver alone, and its grade and stage can only be made with precision by a liver biopsy. The decision to perform a biopsy usually involves assessment of the specific clinical circumstances in a given individual with suspected NAFLD (step 5). The cost and risks of the biopsy are generally weighed against the value of the information obtained from the biopsy in estimating prognosis and guiding future management decisions. If a decision is

Table 4. Conditions Associated With Steatohepatitis

1. Alcoholism
2. Insulin resistance
   a. Syndrome X
      i. Obesity
      ii. Diabetes
      iii. Hypertriglyceridemia
      iv. Hypertension
   b. Lipoatrophy
   c. Mauriac syndrome
3. Disorders of lipid metabolism
   a. Abetalipoproteinemia
   b. Hypobetalipoproteinemia
   c. Andersen's disease
   d. Weber-Christian syndrome
4. Total parenteral nutrition
5. Severe weight loss
   a. Jejunoileal bypass
   b. Gastric bypass[a]
   c. Severe starvation
6. Iatrogenic
   a. Amiodarone
   b. Diltiazem
   c. Tamoxifen
   d. Steroids
   e. Highly active antiretroviral therapy
7. Refeeding syndrome
8. Toxic exposure
   a. Environmental
   b. Workplace

NOTE. All conditions except alcoholism are usually referred to as nonalcoholic steatohepatitis.

[a] Much less common than after jejunoileal bypass.

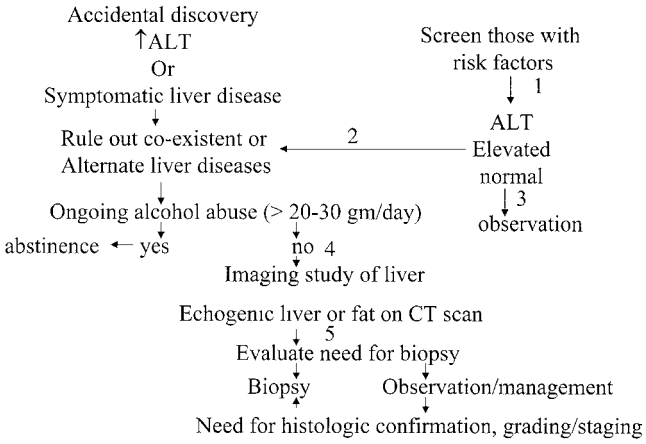

Figure 1. Evaluation of NAFLD.

made not to perform a biopsy, it is advisable to discuss the potential implications with the patient.

Recommendation category: AGA: II, III, IV; AASLD: B, II, III

Evaluation of Prognosis

The prognosis of NAFLD requires assessment of the stage of the disease and the degree of liver dysfunction. Liver function is generally assessed from the serum bilirubin and albumin levels as well as prothrombin time. These usually do not become abnormal unless there is underlying cirrhosis or rapid severe weight loss. Increasing age and body weight as well as diabetes are risk factors for increased hepatic fibrosis. However, the stage of the disease can only be ascertained by a liver biopsy. The decision to perform a liver biopsy to assess the stage of the disease should be weighed against the risks of the biopsy and the impact of the information obtained from the biopsy on future management decisions. If a decision is made not to perform a biopsy, it is advisable to discuss the implications of the decision with the patient.

Recommendation category: AGA: II, III, IV; AASLD: B, II, III

Treatment of NAFLD

Those who are overweight (body mass index >25 kg/m^2) and have NAFLD should be considered for a weight loss program. A target of 10% of baseline weight is often used as an initial goal of weight loss. Weight loss should proceed at a rate of 1–2 lb/wk. Dietary recommendations generally include both caloric restriction and a decrease in saturated fats as well as total fats to $<30\%$ or less of total calories. Although there are no data to support or refute the value of decreasing saturated fats and increasing the fiber content of diet on NAFLD, it is our belief that these interventions may be of value. However, further research is needed to substantiate this opinion. Diet modifications are usually accompanied by a recommendation to exercise regularly. Both intermittent as well as daily exercise can help achieve weight loss and improve insulin sensitivity. The role of pharmacologic agents to induce weight loss in patients with NAFLD has not been studied. Therefore, no recommendation about their safety or efficacy in the management of NAFLD can be made at this time. Those with a body mass index >35 kg/m^2 and NAFLD may be considered for more aggressive weight management, including a gastric bypass. The decision to perform this surgery should take into consideration the morbidity and mortality associated with the procedure as well as the risk of developing subacute nonalcoholic steatohepatitis and liver failure during rapid weight loss. Patients should be monitored for signs of subacute nonalcoholic steatohepatitis during weight loss and liver function checked at intervals depending on the rapidity of weight loss.

Recommendation category: AGA: III, IV; AASLD: D, III

In diabetic individuals, hemoglobin A_{1c} should ideally be brought to $<7\%$. However, the impact of this on NAFLD is not established. There is no specific pharmacologic treatment that has been shown to be effective in the treatment of NAFLD. The clinical alternatives available include vitamin E, ursodeoxycholic acid, and pharmacologic agents that decrease insulin resistance. Although it is common practice to use either vitamin E or ursodeoxycholic acid, there are no data clearly showing their efficacy or comparing the utility of these 2 drugs.

Recommendation category: AGA: IV; AASLD: D, III

References

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2. NHS center for reviews and dissemination: undertaking systematic reviews of research on effectiveness: CRD guidelines for those carrying out or commissioning reviews. CRD report #4. York: University of York, 1996.
3. Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Purpose of quality standards for infectious diseases. Infectious Diseases Society of America. Clin Infect Dis 1994;18:421.

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Abbreviations used in this paper: **AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; NAFLD, nonalcoholic fatty liver disease.**

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