CME

An update on nonalcoholic fatty liver disease

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the accumulation of fat (steatosis) in the liver for reasons other than excess alcohol intake. The diagnosis of NAFLD is becoming more common for a number of reasons, including increased awareness among healthcare providers, improved diagnostic tools, and a greater prevalence of the disorder. This article provides primary care providers with the current understanding of NAFLD, including evidence-based recommendations for managing patients with this common condition.

Keywords: nonalcoholic fatty liver disease, metabolic syndrome, dyslipidemia, adolescent, type 2 diabetes, steatosis

Learning objectives

- Recognize the association between NAFLD and comorbid medical conditions including obesity, dyslipidemia, and diabetes.
- Identify screening and diagnostic testing strategies for NAFLD.
- Describe management approaches for NAFLD.

Nonalcoholic fatty liver disease (NAFLD) is now recognized as the primary cause of chronic liver disease worldwide.[5,14] Although the development of NAFLD may be multifactorial, it is commonly associated with several medical conditions, including obesity, low HDL cholesterol level and elevated triglycerides, and insulin resistance or type 2 diabetes.[1] The disease affects about 30% of adults in the United States, a number that will likely increase as the incidence of underlying conditions increases.[2] Primary care providers are largely responsible for managing patients with this condition. Management traditionally has depended on treating underlying comorbidities because no medication is indicated for the treatment of NAFLD itself.[3-5] However, opinions differ as to how to treat this condition medically, given the contradictory research concerning morbidity and mortality secondary to long-term NAFLD. Recent advances in diagnosis, monitoring, treatment, and prevention of NAFLD have led to a great deal of interest on the part of primary care providers.[2,6]

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PREVALENCE

Although NAFLD is estimated to affect about 30% of US adults, its prevalence varies widely depending on the population being evaluated. For instance, researchers reported greater than 90% prevalence of NAFLD and 5% prevalence of cirrhosis in severely obese patients undergoing bariatric surgery, and an estimated 50% prevalence among patients with dyslipidemia who visited lipid clinics. Overall, they reported that NAFLD occurs most frequently in men, and that Hispanics have a higher prevalence than non-Hispanic whites, who in turn have a higher prevalence than non-Hispanic blacks.[1] Of particular concern is the development and rapid increase of this condition in adolescents. A study by Welsh and colleagues evaluated the prevalence of NAFLD in adolescents (ages 12 to 19 years) over the past 30 years.[7] They found that the prevalence of suspected NAFLD increased from 3.9% to 10.7% among all adolescents in the last 20 years, and from 29.5% to 48.3% among obese adolescent boys. Prevalence was highest (56%) for obese adolescent Mexican American boys. The authors commented on this group's potential effect on healthcare, noting, "this increase represents approximately 2 million additional adolescents with chronic liver disease who are at increased risk of liver failure, cardiovascular disease, and liver cancer in adulthood."[7]

OBESITY A CULPRIT

Much of the surge in cases of NAFLD can be attributed to the epidemic of obesity.[4] The worldwide prevalence of obesity has doubled since 1980, with 400 million patients estimated to have the disorder.[8,9] Additionally, research has shown that the prevalence of both NAFLD and nonalcoholic steatohepatitis (NASH) directly correlates with increases in BMI.[8] Clearly, as the prevalence of obesity escalates, the prevalence of NAFLD and concomitant morbidity and mortality also will rise.[9]

PATHOPHYSIOLOGY

NAFLD rarely occurs in patients without comorbidities, and often is associated with components of metabolic syndrome, specifically abdominal obesity, hypertension, dyslipidemia, and insulin resistance or type 2 diabetes. In many cases, patients with NAFLD will have several of

these conditions. Lomonaco and colleagues discussed the correlation between obesity and NAFLD, explaining that the dysfunctional adipose tissue common in overweight patients leads to the release of excessive free fatty acids and the subsequent accumulation of triglycerides in the liver and other susceptible tissues.[3]

Similarly, Völzke explained the pathogenesis of fatty liver disease in patients with type 2 diabetes, noting that insulin resistance and elevated serum insulin levels ultimately cause increased hepatic absorption and accumulation of triglycerides. In healthy patients, increased fat in the liver triggers the production and secretion of very low density lipoproteins (VLDL), which reduce hepatic lipid levels.[10] However, Finelli and Tarantino explained that this process is impaired in patients with NAFLD, resulting in atherogenic dyslipidemia characterized by elevated serum triglycerides; small, dense, low-density lipoprotein (LDL); and decreased HDL.[4] Other potential associations with underlying NAFLD include hypothyroidism, sleep apnea, and polycystic ovary syndrome.[1]

Certain medications, including amiodarone, antivirals, corticosteroids, methotrexate, tamoxifen, and valproic acid, have been noted to cause hepatic steatosis. Other risk factors for NAFLD include hepatitis C, Wilson disease, parenteral nutrition, starvation, and Werner syndrome.[1,8,10]

DIAGNOSIS

Because patients with NAFLD usually are asymptomatic, the diagnosis often occurs when there is an unexplained increase in liver enzymes, or after an abdominal imaging study reveals evidence of fatty infiltration of the liver. Frequently, the imaging is performed for nonhepatic symptoms in patients with normal liver enzyme levels.

Definitions A variety of diagnostic definitions for NAFLD and NASH can be found in the literature. The practice guideline by the American Association for the Study of Liver Diseases (AASLD), American College of Gastroenterology (ACG), and American Gastroenterological Association (AGA) states that the diagnosis of NAFLD requires two criteria:

- imaging or histologic evidence of hepatic steatosis
- no other cause for secondary hepatic fat accumulation, such as significant alcohol consumption, use of steatogenic medication, or hereditary disorders.[1]

This is similar to the definition put forth by Lazo and colleagues, which is the "presence of moderate to severe hepatic steatosis with normal liver enzyme levels."[2] Lazo and colleagues differentiated NAFLD from NASH by defining the latter as "the presence of moderate to severe hepatic steatosis with increased levels of liver enzymes, in the absence of antibodies to hepatitis B and hepatitis C and without evidence of iron overload."[2]

Because many patients with NAFLD have no diagnosis, researchers and clinicians are interested in determining the appropriate laboratory and imaging studies to identify them.

Key points

- NAFLD is becoming more common among adults and adolescents, and is considered the hepatic manifestation of metabolic syndrome.
- Consider NAFLD when evaluating patients with type 2 diabetes, obesity, and dyslipidemia.
- No drugs are approved to treat NAFLD, so treatment focuses on diet and lifestyle modifications and addressing comorbid conditions.

Diagnosis of a patient with suspected NAFLD includes evaluating and eliminating other conditions that cause chronic liver disease, including iron or copper storage disease, chronic viral hepatitis, and chronic autoimmune hepatitis. The American Academy of Pediatrics Expert Committee recommends biannual evaluation of liver enzymes in overweight and obese children starting at age 10 years.[11] No screening guidelines for NAFLD exist for adults, even adults in higher-risk groups. One reason is that liver biochemistries can be normal in patients with NAFLD and NASH. In addition, the degree of liver enzyme elevation does not accurately correlate with the degree of inflammation or fibrosis.

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Serum ferritin is a novel marker that may determine fibrosis and histological severity in patients with NAFLD. One study compared serum ferritin levels with histology of liver biopsies, finding that elevated serum ferritin correlated with worsened histological activity.[12] The authors concluded that serum ferritin was a predictor of advanced fibrosis in patients with NAFLD, and suggested using this marker in the management of these patients.

Cytokeratin-18 is another investigational biomarker for the presence of liver inflammation in patients with NAFLD. Although results are promising, this test is not commercially available.[1]

Liver biopsy is the accepted standard for diagnosing NAFLD.[1,3,10,13,14] Although biopsy allows for staging and provides prognostic information, this test has some notable drawbacks. Because NAFLD does not affect the liver equally, sampling error may occur. In addition, the test is costly, invasive, and associated with morbidity and (rarely) mortality.[13]

Alternative noninvasive diagnostic tests, including ultrasound, CT, and MRI, identify fatty infiltration of the liver, but do not provide information on inflammation or fibrosis.

Ultrasound is often preferred because of its lower cost, although it has limited usefulness in patients with higher BMIs. A newer approach has been to combine ultrasound with xenon-133 scanning. Xenon-133 is a radioactive gas typically used for lung ventilation studies, but the gas also is absorbed by the liver. When compared with ultrasound alone, this novel combination was similarly cost-effective but more accurate in quantifying hepatic steatosis, even in patients with higher BMIs.[13]

Other promising diagnostic tools being studied for the measurement of liver fibrosis include transient elastography and magnetic resonance elastography. The limitations of these methods include poor results in patients with higher BMIs and clinical availability, respectively.[1]

TREATMENT

No medication is specifically indicated to treat NAFLD, and management of this condition has largely targeted the associated comorbidities. Management strategies may vary but typically involve medication along with dietary and lifestyle modifications.

Statins Because of the association of dyslipidemia and CVD, statins typically are prescribed for patients with NAFLD. Initially, prescribing statins to patients with NAFLD was controversial because the drugs can cause elevated AST or ALT in 1% to 3% of patients.[3] However, the AASLD, ACG, and AGA practice guideline addressed the use of statins in patients with NAFLD, stating that statins infrequently cause serious liver injury in clinical practice. In support of this comment, the guideline authors summarized several studies, including one randomized controlled trial, which concluded that statins are safe in patients with liver disease, and that patients with NAFLD are not at increased risk for hepatic injury from statins.[1] However, the long-term benefits of statins in patients with NAFLD have not been rigorously studied. These guidelines described only one post-hoc analysis of a study on cardiovascular outcomes, which found that "statins significantly improve liver biochemistries and cardiovascular outcomes in patients with elevated liver enzymes likely due to NAFLD."[1] Overall, the guideline recommends using statins to treat dyslipidemia in patients with NAFLD.[1]

Medications for diabetes Research on treatment using medications for diabetes in patients with NAFLD has largely focused on metformin and pioglitazone. A small pilot study by Hajiaghamohammadi and colleagues randomized patients with NAFLD to receive either pioglitazone or metformin, and monitored their biochemical indices over 2 months.[15] Both agents produced significant improvements in fasting blood sugar and liver transaminases along with moderate improvements in triglycerides, cholesterol, and insulin. Although this study did not demonstrate histological improvement, the authors called for longer studies on these medications in order to determine additional benefits.[15]

Chalasani and colleagues added that a meta-analysis of five randomized controlled trials of pioglitazone demonstrated significant improvement in steatosis and inflammation, but no such improvement in fibrosis. Their recommendation was to use pioglitazone in the treatment of steatohepatitis in patients with biopsy-proven NASH.[1]

Other agents Extensive studies of vitamin E demonstrated only modest improvement in the NAFLD Activity Score (NAS) in patients with NAFLD. The NAS is a composite of inflammation, steatosis, and ballooning scores used to measure changes in liver histology in patients with NAFLD. Current recommendations are to prescribe vitamin E at a dose of 800 IU/day for patients with biopsy-proven NASH who do not have diabetes.[3]

Di Minno and colleagues reviewed the use of omega-3 fatty acids in treating NAFLD.[5] They discussed a number of small studies, which demonstrated beneficial effects on triglycerides, liver enzymes, fasting glucose, and liver fat content.[5] Larger, randomized controlled trials must be done before omega-3 fatty acids can be recommended for the treatment of NAFLD, but current guidelines suggest practitioners should consider them as first-line agents for the treatment of hypertriglyceridemia in patients with NAFLD.[1]

Lifestyle modifications, such as caloric restriction, reduction in dietary fat and carbohydrate composition, and physical activity, have proven effective at reducing liver enzymes and degree of hepatic steatosis in a number of studies. One 48-week study incorporated all of these modifications in patients with steatohepatitis. Compared with controls, these patients lost an average of 9.3% of body weight and had significant improvements in steatosis, inflammation, and NAS.[16] Additional studies have demonstrated that patients who increased their exercise levels yet did not lose body weight still had significant reduction in hepatic fat. Given the limited duration of these studies, however, the investigators could not reach conclusions about long-term morbidity or mortality. Finelli and Tarantino supported this view, noting, "There is no consensus as to what diet or lifestyle approach is the right one for NAFLD patients, likely because of a lack of scientific evidence."[17] Among other suggestions, they recommended a diet that contained omega-3 fatty acids; fruits and vegetables; and low-glycemic-index, high-fiber foods; and reduced consumption of saturated fats, simple carbohydrates, and sweetened drinks. The same authors addressed the effects of exercise on NAFLD in a

> One study found that patients with NAFLD who had normal liver enzymes were still at risk for severe, progressive liver disease.

separate article, advocating for a combination of aerobic and resistance exercise three to four times per week to be effective in improving the metabolic profile of patients with NAFLD.[4] Treatment guidelines suggest a weight loss of 3% to 5% to improve hepatic steatosis, and that a greater weight loss could significantly improve NAS.[1]

CONSEQUENCES

Researchers are still evaluating the long-term consequences of NAFLD. Initially, this was thought to be a relatively benign disease with minimal histological progression. Supporting that theory is the prospective cohort study by Lazo and colleagues, which investigated all-cause mortality, cardiovascular disease, cancer, and liver disease in US adults with NAFLD.[2] They found no increase in mortality in patients with NAFLD over the 14.5-year follow-up period.[2] The authors admit a limitation of the investigation was its relatively small sample size, and that the follow-up duration may not have been long enough to capture all liver-related mortality. Wattacheril and Chalasani reviewed the Lazo study and described a number of other projects investigating the long-term effects of NAFLD.[6] They concluded that "NAFLD is a serious condition only in a subgroup of individuals and the challenge is to precisely identify those at risk for increased morbidity and mortality."[6] Clearly, some patients may progress from NAFLD to NASH to cirrhosis to hepatocellular carcinoma (**Figure 1**). Identification of these at-risk patients has proven to be difficult due to a lack of noninvasive, cost-effective tools.

Other researchers agree that NAFLD is associated with increased morbidity and mortality. One study by Fracanzani and colleagues found that patients with NAFLD who had normal liver enzymes were still at risk for severe, progressive liver disease.[18] The researchers reported identifying NASH in more than 50% of the patients they evaluated who had NAFLD, normal ALT, and either elevated serum ferritin or chronic hepatic steatosis. Unfortunately, other studies have noted that 10% to 29% of patients with NASH developed cirrhosis within 10 years, and up to 27% of patients with cirrhosis due to NASH eventually developed hepatocellular carcinoma.[5] Bouziana and Tziomalos noted that patients with NAFLD had higher mortality, mainly due to liver and cardiovascular disease, compared with the overall population.[14] Discussing the costs associated with this condition, Völzke estimated that over a 5-year period, patients with NAFLD will incur 26% higher healthcare costs than those without it.[10] Additional studies are required to further clarify the effect of NAFLD on morbidity, mortality, and healthcare costs.

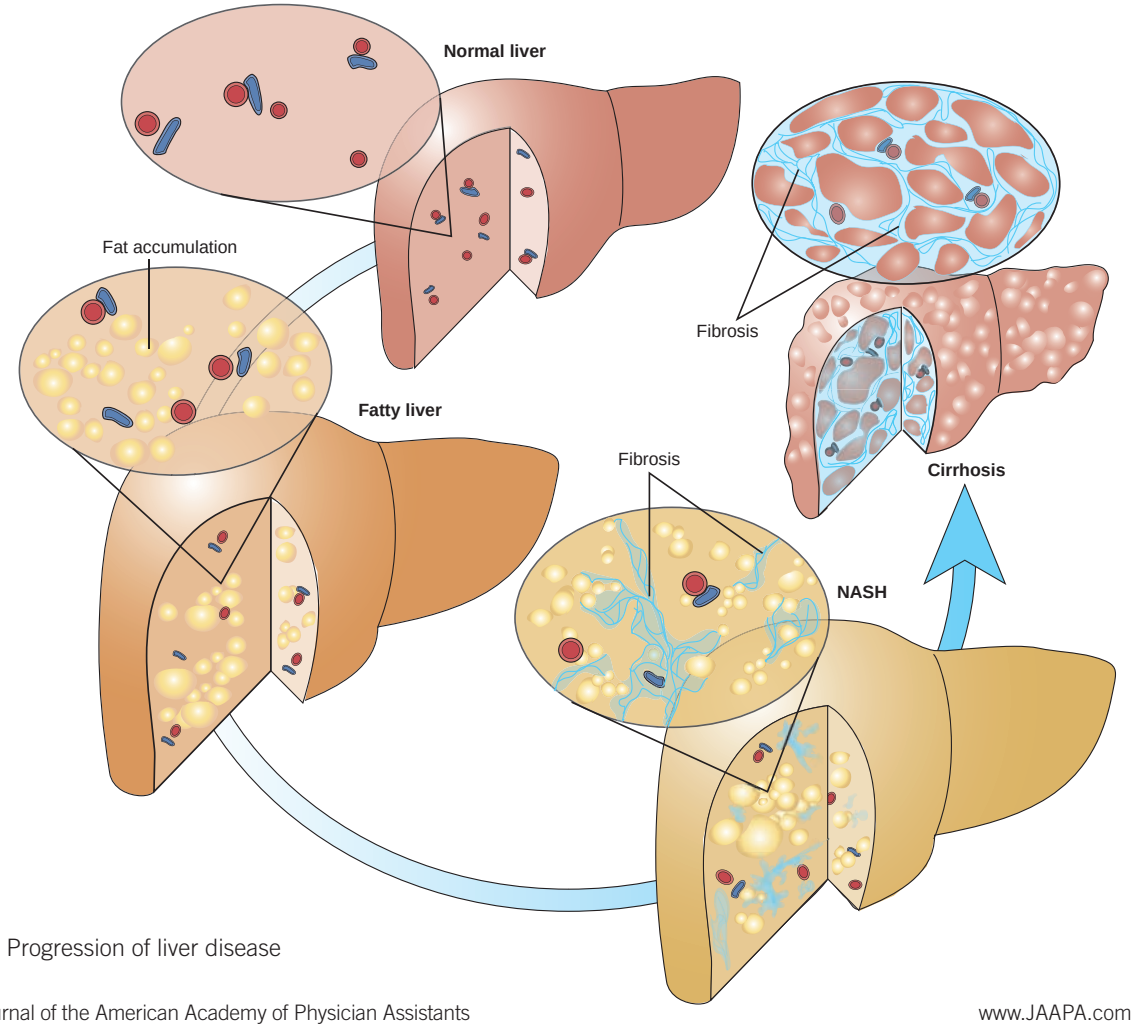

FIGURE 1. Progression of liver disease

SUMMARY

NAFLD, a common condition encountered by primary care providers, may have significant long-term consequences. This condition is increasingly prevalent in adults and adolescents. NAFLD is considered to be the hepatic manifestation of metabolic syndrome, and it is commonly associated with type 2 diabetes, obesity, and dyslipidemia. Although clinicians should consider NAFLD whenever a patient receives a diagnosis of metabolic syndrome, normal-weight patients and those with normal biochemical indices may also have NAFLD. Diagnostic criteria vary and may include biochemical markers and characteristic imaging findings, but histological evaluation through liver biopsy remains the standard for diagnosis. No medications are approved to treat NAFLD. Management consists of dietary and lifestyle modifications and medications targeting underlying comorbid conditions such as dyslipidemia and diabetes. Evidence suggests that patients with NAFLD have increased morbidity, mortality, and treatment costs. Additional studies are needed to further clarify the underlying pathogenesis of this condition and improve tools to identify, treat, and prevent NAFLD. **JAAPA**

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