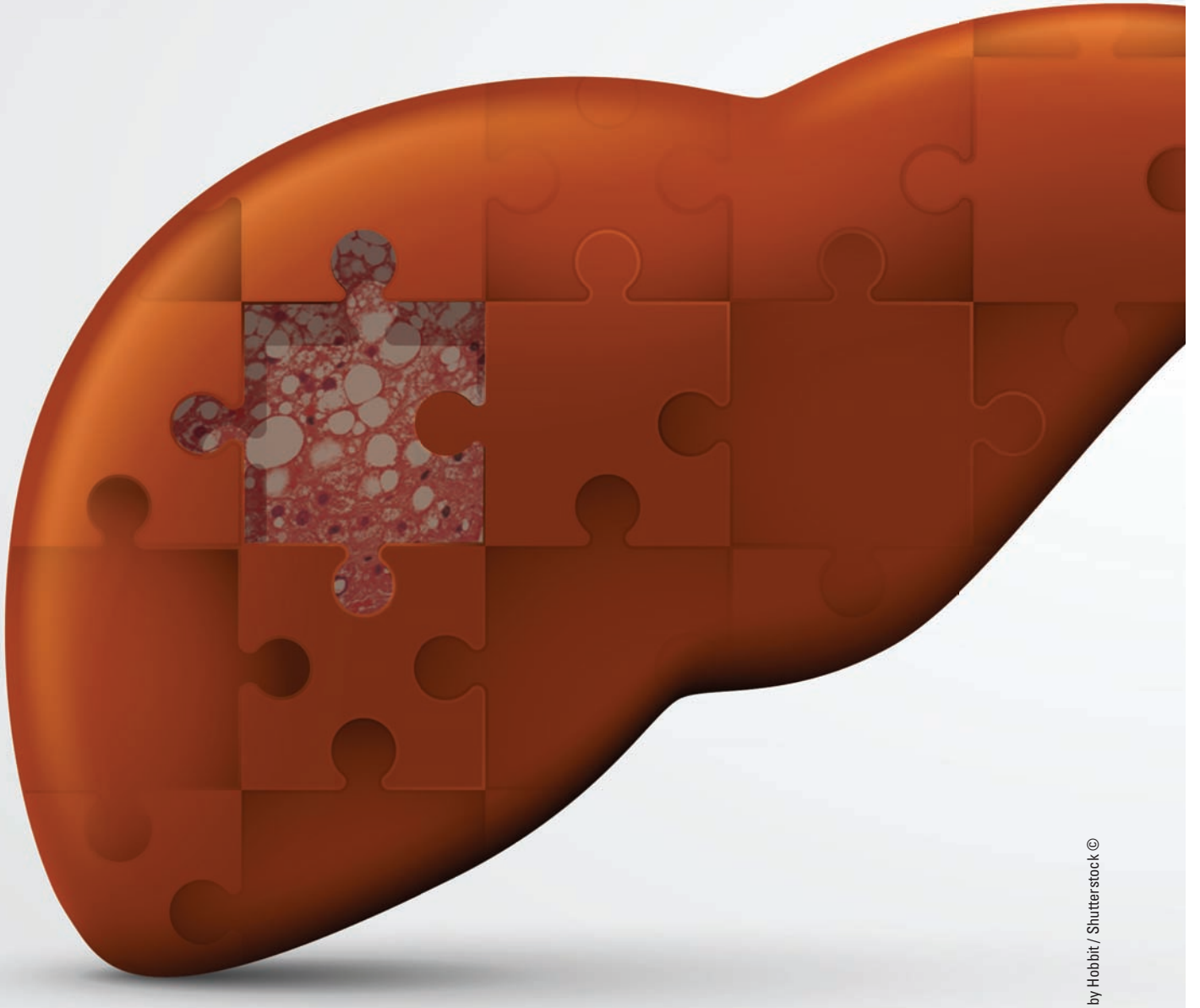
Treating the patient with nonalcoholic



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fatty liver disease

Abstract: Nonalcoholic fatty liver disease (NAFLD) is becoming a worldwide health crisis. It is important for NPs to understand the spectrum of NAFLD. Although lifestyle modifications are the first-line treatment, the NP should be aware of current and future medication management to help the patient live a healthy life.

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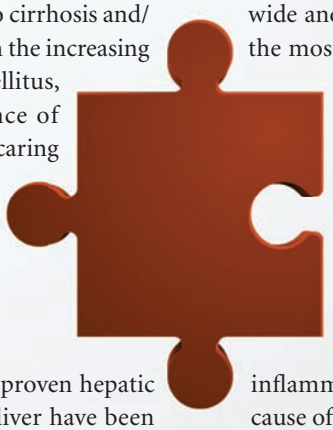
Nonalcoholic fatty liver disease (NAFLD) covers a wide spectrum of fatty liver issues, ranging from simple fatty infiltration in liver cells (hepatocytes) to nonalcoholic steatohepatitis (NASH), to cirrhosis and/or hepatocellular carcinoma (HCC).[1] With the increasing prevalence of obesity, type 2 diabetes mellitus, and metabolic syndrome, the prevalence of NAFLD is also increasing, and NPs will be caring for these patients more frequently.[2] This article seeks to improve the understanding of the spectrum of NAFLD and provide up-to-date treatment recommendations.



Background and prevalence of NAFLD

NAFLD is defined as biopsy- or imaging-proven hepatic steatosis, in which other causes of fatty liver have been excluded, including alcoholic liver disease, genetic diseases, or medication-related causes.[3,4] (See *Definition of significant alcohol consumption.*) NAFLD should be considered as a diagnosis in patients who have had other causes of liver disease excluded and who have one or more risk factors for NAFLD (see *Risk factors for development of NAFLD*).

Ninety percent of patients with NAFLD have one or more of the following risk factors: obesity, insulin resistance, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, elevated triglyceride levels, and/or low high-density lipoprotein levels.[3-5]

The prevalence of NAFLD is approximately 20% worldwide and 25% in Western countries, making it one of the most common causes of liver disease.[2-4,6] NAFLD occurs in one in three individuals in the developed world and is more common in patients with severe obesity and diabetes.[3,7,8] Mortality and disease evolution to fibrosis or cirrhosis is increased in older patients with NAFLD.[3]

Cardiovascular disease-related events are the most common causes of mortality in patients with NAFLD.[3] NASH, which is a progression from simple fatty liver disease to inflammation and injury, is the third most common cause of liver disease requiring a liver transplant in the United States.[3,4,7] According to Charlton and colleagues, by 2020, NASH will be the leading cause of liver transplant in the United States.[9] Patients with NASH can progress to cirrhosis and/or HCC.

Pathophysiology of NAFLD

The pathophysiology of NAFLD is complex and not completely understood. Day and James sought to describe the process of fatty liver disease progression as the "two hits

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theory.[12]" In the first hit, steatosis, or fatty infiltration in the liver, occurs from issues with insulin resistance and fatty acid metabolism.[2,10-12] Increased free fatty acid to the liver causes hepatic steatosis. Insulin resistance increases lipolysis from adipose tissue. This process leads to release of proinflammatory cytokines (tumor necrosis factor [TNF]-alpha and interleukin-6), oxidative stress, and inflammation.[13] These, along with molecular endotoxins and genetic factors, are thought to contribute to the second hit.[2,4,14,15] The second hit results in oxidative stress and steatohepatitis.[12]

Dietary choices can also play a part. With high amounts of cholesterol to the liver (either from diet or genetics), fatty acids are converted to nontriglyceride metabolites. These particles contribute to hepatocyte injury. High consumption of sugar—particularly fructose—reduces intracellular adenosine triphosphate and is converted to fat, which is deposited in the liver.[5] Collagen is deposited in the liver and causes fibrosis as inflammation and liver injury occur.[4] As this process continues, fibrosis can turn into cirrhosis and/or HCC. As the hepatocytes become fatty, patients are at higher risk for developing diabetes mellitus, cardiovascular disease, and complications related to these diseases.[7]

Diagnosing NAFLD

It may be difficult to know when to suspect NAFLD, since most patients are asymptomatic.[4,5,7] Some symptoms that present are vague, including abdominal discomfort, fatigue, and nausea.[2] Higher-risk patients include patients who have type 2 diabetes mellitus and who are obese. These patients are not only at higher risk for liver disease progression but also cardiovascular disease and death.[7] There is currently no diagnostic screening tool or recommendations for screening for NAFLD in primary care, even if a patient has several risk factors to suggest this disease.[3] In most cases, NAFLD is found incidentally when a patient has elevated liver enzymes or when it is seen on radiologic imaging studies as hepatic steatosis.[2,4]

History. A complete history should be obtained in the patient who has liver disease when NAFLD is suspected. Occasional symptoms that may occur include right upper quadrant abdominal pain, pruritus, and jaundice. Generally, the patient is without symptoms. Other etiologies of liver disease should be excluded. Current lifestyle and dietary habits, including alcohol consumption history, should be noted. Social history should include current or prior intravascular or other illicit drug use, blood transfusions, and sexual activity.[4]

Physical exam. Physical exam should include vital signs, height, weight, body mass index (BMI), BP, and waist circumference. Hepatosplenomegaly may be present if the patient has evidence of portal hypertension.[2,4] Dorsocervical lipohypertrophy, an increased amount of fat distribution along the cervical spine, may be present and has been noted in patients with NASH.[16]

Lab findings. Labs to exclude other causes of liver disease include: total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, albumin, total bilirubin, hepatitis B surface antigen, hepatitis C antibody, ferritin, iron, fasting blood glucose, hemoglobin A1C, lipid panel, and low-density lipoprotein cholesterol, prothrombin time, and insulin levels.[4]

Patients with NAFLD commonly have elevated ferritin levels, and 20% have elevated uric acid levels.[2,3] Most patients with NAFLD will have a mild elevation of AST and ALT, although some will be normal.[2] There are no imaging or biomarker tests that can differentiate between hepatic steatosis and NASH.[8] Cytokeratin-18 fragment levels are the most researched tool to predict NASH, which is an indicator of hepatocyte apoptosis.[7]

Radiologic findings. Imaging studies to evaluate for NAFLD could include ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). Ultrasound cannot identify inflammation or fibrosis, but it is the first imaging study done to evaluate for hepatic steatosis, for which it has a sensitivity of 60% to 94% and specificity of 66% to 97%.[4,7] It is inexpensive and extensively available. CT scan can be done to assess the structure of the liver.[4] It is an option for determining hepatic steatosis; however, there is significant radiation associated with this imaging study.[7] MRI is accurate for quantifying the extent of hepatic steatosis, but it is expensive.[4] Magnetic resonance spectroscopy is accurate in identifying steatosis and has the potential to become an ideal test for grading and determining the

Definition of significant alcohol consumption[3]

Men
Greater than 21 drinks per week over a 2-year period

Women
Greater than 14 drinks per week over a 2-year period
1 drink = ~10 g alcohol

Risk factors for development of NAFLD[3,4,8]

- Age, older than 45
- Diabetes mellitus
- Hispanic ethnicity
- Portal hypertension
- Insulin resistance
- Metabolic syndrome
- Obesity
- Family history significant for metabolic syndrome, cardiovascular disease, chronic liver disease

presence of steatosis; however, it is costly and with limited availability.[7]

Noninvasive measures. Risk scores, such as the NAFLD fibrosis score and the NASH test, have been used to try to determine patients who have NASH but can be inaccurate (see *Noninvasive fibrosis scoring tools*).[5,17-19] Transient elastography is a newer imaging study on the horizon. Described as a pulse-echo ultrasound, it has shown usefulness in determining the presence of fibrosis. This may be helpful in determining if liver biopsy is necessary.[7]

Liver biopsy. Liver biopsy is the gold standard for determining if NAFLD is present and for staging severity of disease.[7] Complications, including bleeding and infection, occur in 1% to 3% of patients; death occurs in 0.01% of patients.[7] Misdiagnosis can occur in many cases. Staging and diagnosis are subjective and can vary by the pathologist.[7] Additionally, there is a higher risk of complication and difficulty obtaining an adequate sample in patients who are obese.[7]

A liver biopsy should be considered in patients with highly elevated liver function tests (LFTs) or patients with elevated LFTs and a normal BMI.[4] The pathology report may include findings indicative of NAFLD such as: Mallory hyaline, hepatocyte ballooning, and lymphocytic and neutrophilic inflammatory infiltrate in perivenular areas. Other findings may state hepatocyte necrosis, apoptosis, and degree of fibrosis—graded and staged.[4,8]

Noninvasive fibrosis scoring tools[5,17,18]

Scoring tool	Components	Scoring
NAFLD fibrosis score[17]	Calculation using age, platelet, ALT, AST, and albumin levels, BMI, glucose intolerance or diabetes mellitus	• <-1.455: predictor of absence of significant fibrosis • ≤-1.455 to ≤0.675: indeterminate score • >0.675: predictor of presence of significant fibrosis
NASH test[18]	Calculation using lab values including alpha$_2$-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, gamma-glutamyl transpeptidase, fasting blood glucose, triglyceride level, cholesterol, ALT and AST, and age, gender, weight, and height.	Scoring is established into one of three groups: N0: No Nash N1: Borderline N2: Nash

NAFLD treatment options

Patients with NAFLD without liver injury have an excellent prognosis, and their management is primarily aimed at prevention and reversal of hepatic injury and fibrosis.[3-5] The aim is to prevent progression to cirrhosis and HCC if NASH is present, thereby avoiding cirrhosis complications.[2,20] Managing other comorbidities including dyslipidemia, sleep apnea, hypertension, diabetes mellitus, and obesity is essential.[3-5] Unfortunately, there is no pharmacologic treatment for NAFLD.[2,20] Primary care considerations include ensuring hepatitis A and B immunizations and recommending elimination of alcohol consumption.[4] Some specialists are supportive of more intensive management of patients with diabetes mellitus and NAFLD.[7] Targher and colleagues note that NAFLD is an independent risk factor for cardiovascular disease, so careful and prompt disease management is essential for an optimal patient outcome.[21]

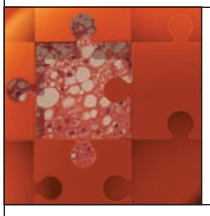
Lifestyle changes. Initial treatment should include lifestyle changes, such as increased physical activity, a low cholesterol/low-fat diet, decreased caloric consumption, avoidance of trans fats, and weight loss.[3-5,8] Lifestyle modifications not only have the potential to improve liver disease but can also improve common comorbidities (for example, hypertension, diabetes, and hyperlipidemia).[20]

Diet and exercise. Current recommendations include decreased caloric consumption, increased physical activity, and weight loss. The Mediterranean diet has shown improvement in hepatic steatosis and insulin sensitivity in NAFLD patients.[22,23] Encouraging a reduction in calories along with good food choices is recommended. Dietary changes should include complete avoidance of high-fructose corn syrup and trans fats, as these dietary choices are associated with hepatic steatosis development and insulin resistance.[8] Patients with NAFLD should not consume alcohol.[3] Interestingly, some studies have been performed supporting that coffee consumption is associated with reducing hepatic fibrosis. One or two cups of unsweetened coffee can be seen as a benefit in patients with NAFLD.[24-26]

Weight loss of 3% to 10% can improve disease progression and normalization of AST levels, but weight gain can lead to NASH recurrence.[3-5,27] Hepatic steatosis can be reduced with even a 3% weight loss.[3,28] Exercise, both with and without weight loss, has shown benefits for the patient with NAFLD.[29,30] Patients should be made aware that exercise with reduction in caloric intake will likely lead to weight loss, and even a small amount of weight loss will be extremely beneficial to liver improvement.[20] There is positive evidence that exercise will decrease liver steatosis.[6,31]

Behavioral changes. Behavioral changes and psychosocial therapy can assist in helping the patient make necessary

lifestyle changes.[8] Engaging the patient in his or her care is important for patient success. Identifying patient struggles, establishing short- and long-term goals, and supporting patient's self-esteem can help the patient be successful. Making the patient aware of the benefits of these lifestyle changes can help. Supplying the patient with adequate resources is important for self-monitoring of dietary intake and exercise activity. A support group of other patients who have had similar experiences and successes is helpful. Patients should have return visits to monitor and encourage progress. Other resources to consider include consultation with a dietitian and psychologist.



Omega-3 fatty acid is recommended to treat hypertriglyceridemia, a common comorbidity of NAFLD.

As mentioned above, alcohol consumption should be stopped. Some patients may find this challenging and may need additional support to accomplish this goal, including social work support and/or joining a support group.

Prescription medications. Studies have been conducted to see if metformin administration is associated with improved liver histology, but it is not recommended for treatment of NASH.[3,8,32] Thiazolidinediones have been shown to improve the sensitivity of insulin and have some anti-inflammatory and antiatherosclerotic properties.[20] Research has shown improvements in liver steatosis.[32-36] The study (PIVENS), Pioglitazone versus Vitamin E versus Placebo for Treatment of Non-diabetic Patients with Nonalcoholic Steatohepatitis, showed that nondiabetic patients with NASH taking pioglitazone and vitamin E saw decreased hepatic inflammation; fibrosis was not affected.[36] Pioglitazone has been studied for NASH treatment; however, long-term use and safety have not been established.[1,5] Therefore, it is not considered a treatment strategy for management of NAFLD (including NASH) due to its adverse reactions, which include weight gain, death from cardiovascular events, and osteoporosis.[37] Rosiglitazone has very restricted use in the United States because of its association with increased risk of coronary events.[5] The majority of patients with NASH in these studies did not have diabetes.[3]

Ursodeoxycholic acid has been investigated in the treatment of NAFLD. It is a cytoprotective agent that reduces proinflammatory cytokines and prevents cellular apoptosis.[2] Current research does not recommend its use.[3,8,38-40] Other medications researched in the treatment of fatty liver included: orlistat, gemfibrozil, Vitamin C, betaine, n-acetylcysteine, and sibutramine.[41-47] However, none have been deemed safe for the treatment of NAFLD.

Over-the-counter medications. Vitamin D deficiency has been found to be an independent factor associated with NAFLD and the severity of NASH.[48] Vitamin D levels should be monitored and maintained. Disease progression and liver injury are caused by oxidative stress in patients with NASH. Due to this knowledge, antioxidants—particularly vitamin E—are thought to improve liver disease in patients with NAFLD.[3] Vitamin E is not recommended for patients with diabetes who have NASH, NAFLD without liver biopsy, NASH cirrhosis, or patients with cryptogenic cirrhosis.[3] Miller and colleagues performed a meta-analysis that determined a rise in all-cause mortality in patients taking high-dose vitamin E (doses of 400 international units/day). Although vitamin E has few noted adverse reactions, results of this meta-analysis should not be overlooked. It should be prescribed cautiously.[13,49,50]

Omega-3 fatty acid supplements have also been investigated in the treatment of NAFLD. These supplements are not recommended to treat NAFLD; however, they are recommended for treatment of hypertriglyceridemia, a common comorbidity of NAFLD, and can be given in those cases.[3] Increasing intake of omega-3 fatty acids has been documented to reduce hepatic steatosis and is an option for overall cardiovascular health.[8,51] Benefits are seen in supplement doses less than 1 g/day; however, there have not been any controlled trials establishing the degree of improvement in hepatic steatosis or the ideal dosage.[51] Research has noted that probiotics decrease aminotransferases and improve liver histology by decreasing gastrointestinal bacterial overgrowth (a contributor of oxidative stress).[52,53] A meta-analysis by Ma and colleagues noted that probiotics can improve insulin resistance, liver aminotransferases, total cholesterol, and decrease TNF-alpha in patients with NAFLD.[54] More studies are needed to determine proper dosing.[13]

Other options. Bariatric surgery is not recommended as a treatment for NAFLD or NASH, but it has been noted that patients who have undergone bariatric surgery have seen improvement in liver histology.[3] Patients with NAFLD and dyslipidemia should be on an HMG-CoA reductase inhibitor (statin) to treat their dyslipidemia, given there are no contraindications. Several research studies have stated that there is no evidence to suggest statins will cause liver injury.[3,8,55-57] Patients with cirrhosis from NAFLD should undergo screening for HCC and esophagogastroduodenoscopy for gastroesophageal varices.[3] Hepatology consultation should be requested, preferably

to a transplant center. There is no need for routine liver biopsy to evaluate the progression of the disease.[3]

Understanding NAFLD

NAFLD encompasses a range of nonalcohol-related liver disease extending from simple fatty permeation of the liver cells to inflammation (NASH) to cirrhosis.[8] It is essential that NPs understand the complexity of NAFLD. Unfortunately, medication management of NAFLD is limited. More research is needed to find new treatment modalities. Behavioral therapy, including dietary and physical activity changes, has been shown to improve liver disease. NPs are key providers to help and guide this select group of patients to a state of better health.

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- You will receive your CE certificate of earned contact hours and an answer key to review your results. There is no minimum passing grade.
- Registration deadline is November 30, 2017.

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