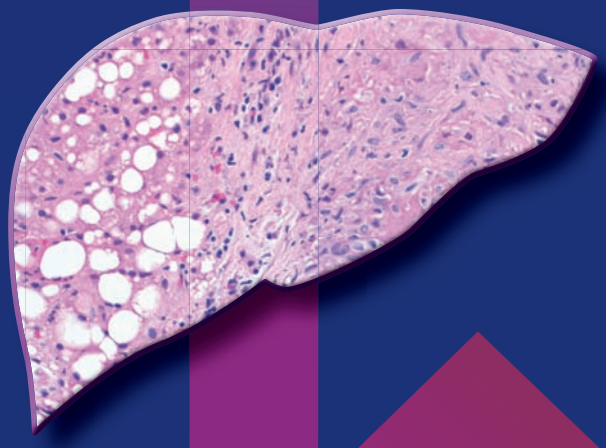
The rising incidence



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# of nonalcoholic fatty liver disease

Abstract: Nonalcoholic fatty liver disease (NAFLD) is the leading cause of liver disease in the United States and will soon be the leading indication for liver transplantation. NAFLD can lead to cirrhosis of the liver and is usually asymptomatic. Prompt referral to a hepatologist may halt the morbidity and mortality associated with NAFLD.

By Jessica Wisocky, MSN, CNP and Sonali Paul, MD, MS

Nonalcoholic fatty liver disease (NAFLD) is an umbrella term used to describe a spectrum of liver diseases ranging from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH). NAFLD is characterized as "evidence of hepatic steatosis either by imaging or histology without known causes for secondary hepatic fat accumulation, such as significant alcohol consumption, use of steatogenic medication, or hereditary disorders."[1]

While NAFL has historically been considered a benign condition, NASH has the potential to cause inflammation and fibrosis of the liver. NASH can be progressive in nature, leading to fibrosis and even cirrhosis of the liver, hepatocellular carcinoma, and liver transplantation.[2] The development of NAFLD is closely associated with obesity and metabolic syndrome, and the prevalence of this chronic liver disease is on the rise.[1]

The most recent statistics from the CDC estimate the prevalence of obesity in the United States is over 36%.[3] With obesity rates on the rise, an increasing number of patients are being diagnosed with obesity-associated medical conditions, such as type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension, which in constellation make up metabolic syndrome.

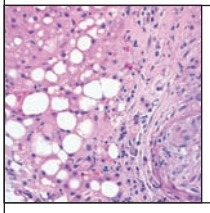
As the prevalence of weight-associated diseases increases, so does the incidence of NAFLD. It is estimated that 75% of patients who are overweight and 90% to 95% of patients who are morbidly obese are afflicted by NAFLD.[4] NAFLD is often described as the liver's manifestation of metabolic syndrome and is the result of triglyceride accumulation in the liver.[5] NAFLD is the leading cause of liver disease in the United States and will likely surpass hepatitis C as the leading indication for liver transplantation.[6,7]

The liver plays a key role in lipid metabolism by importing free fatty acids (FFAs) and manufacturing, storing, and exporting lipids.[8] Under normal conditions, FFAs found in the liver are oxidized and converted into

Keywords: fatty liver disease, metabolic syndrome, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, steatosis

triglycerides and ultimately secreted from the liver as very low-density lipoprotein.[9] Hepatic steatosis arises from dietary intake, breakdown of visceral fat, and de novo lipogenesis.[10] De novo lipogenesis and lipolysis of visceral fat are impacted by insulin resistance and are associated with obesity and T2DM.[10]

Patients who are obese tend to suffer from insulin resistance and/or dyslipidemia (in particular, hypertriglyceridemia), which can result in excess circulating FFAs. Chronically elevated levels of FFAs give rise to metabolism dysregulation, resulting in an imbalance of lipid deposition and removal in the liver, ultimately causing triglyceride deposition and hepatic steatosis.



NASH can be progressive in nature, leading to fibrosis and cirrhosis of the liver, and hepatocellular carcinoma.

The presence of hepatic steatosis increases morbidity and mortality from cardiovascular disease, extra hepatic manifestations of metabolic syndrome (such as worsening insulin resistance, increased abdominal obesity, and hypertriglyceridemia), and complications directly related to liver disease.[7] In patients with NASH, not only is steatosis required, but there should be damage to the hepatocytes with inflammation and ballooning (injury).[5,11]

Pathophysiology

The exact mechanism by which hepatic steatosis progresses into NASH is not well understood, but it is believed to be multifactorial in nature. It is a commonly held notion that NASH develops in the setting of systemic inflammation secondary to an increase in tumor necrosis factor (TNF) alpha, oxidative stress, and mitochondrial dysfunction, which give rise to a proinflammatory state that has the propensity to mediate liver damage.[7-9,12] The various components of metabolic syndrome promote a proinflammatory state that works to perpetuate metabolic dysregulation and systemic inflammation.[7]

Obesity has been associated with increased circulating cytokines, such as TNF, while insulin resistance has been shown to bolster levels of circulating FFAs, which promote a proinflammatory state and increase the rate of insulin resistance.[7] A symbiotic relationship ensues where obesity stimulates metabolic dysfunction and the deposition of steatosis in the liver, which fosters further metabolic dysregulation and a proinflammatory state that then promotes the transition of simple steatosis into steatohepatitis.[13]

Clinical manifestations

Most cases of NAFLD are found incidentally during imaging studies obtained for other reasons. Most patients are asymptomatic, but some may complain of intermittent upper-right quadrant pain, dyspepsia, or fatigue.[9,14] Elevated liver function tests (LFTs) can been seen in patients with NAFLD, with alanine aminotransferase (ALT) usually slightly more elevated than aspartate aminotransferase (AST) and the AST/ALT ratio being less than 1; however, about 80% of patients will not have abnormal LFTs.[9,14]

Approximately 25% of patients with NAFLD will also have a positive antinuclear antibody or smooth muscle antibody, and up to 50% of patients with NAFLD will have elevated serum ferritin.[1,9,14-16] The positive autoimmune antibodies have not been shown to correlate with more advanced liver disease.[15,16] However, hyperferritinemia (ferritin levels greater than 1.5 times the upper limit of normal) has been shown to correlate with liver fibrosis severity.[9,17,18]

Patients often present with a body mass index (BMI) over 30 kg/m^2 and have a diagnosis of T2DM or pre-T2DM, hypertension, and dyslipidemia.[9,14,19] There is also emerging data that suggest women with polycystic ovary syndrome (PCOS) may be at increased risk for developing NAFLD; due to the proinflammatory state of PCOS, this may also increase their risk of developing NASH.[13,20-22] Recent studies have linked the presence and severity of obstructive sleep apnea (OSA) to the severity of NASH.[13,23,24]

OSA leads to hypoxia, which stimulates insulin resistance and lipogenesis, resulting in a proinflammatory state that is accompanied by the production of cytokines and TNF alpha.[25] The hypoxic state secondary to OSA has been linked to the stimulation of vascular endothelial growth factor and collagen deposition in the liver, resulting in fibrosis.[25] Early on in the disease process, hepatomegaly may be seen on physical exam.[9] Patients with advanced fibrosis secondary to NASH can present with clinical findings of cirrhosis, which can include splenomegaly, thrombocytopenia, palmar erythema, spider angioma, gynecomastia, ascites, and jaundice.[9,19]

Diagnosis and evaluation

NAFLD can be diagnosed by noninvasive means, such as ultrasound, computed tomography scan, or magnetic resonance imaging, in which steatosis or fatty infiltrate of the liver is seen.[12] However, the gold standard diagnostic test for assessing NAFLD is a liver biopsy.[1] A liver biopsy differentiates NAFL from NASH and stages the degree of liver fibrosis. On liver biopsy, NAFL presents as steatosis,

occupying more than 5% of the hepatocytes.[2] The inflammation seen on NASH liver biopsies and the associated cell damage can result in fibrosis or scarring of the liver. NASH is considered a progressive disease that can lead to cirrhosis of the liver, hepatocellular carcinoma, and the need for liver transplantation.[2] (See *Liver biopsy in a patient with NASH*.)

However, liver biopsies are invasive, carry a risk of complications (including pain and bleeding), and are cost-prohibitive.[1,5] Recently, efforts have been made to stratify patients based on risk of having more advanced disease, as measured by increased fibrosis, for referral to liver biopsy.

The combination of metabolic syndrome and steatosis of the liver has been shown to be a strong predictor of the presence of steatohepatitis and is correlated with increased risk of advanced fibrosis of the liver.[1] According to the American Association for the Study of Liver Diseases (AASLD) treatment guidelines, a liver biopsy is warranted in patients with metabolic syndrome and NAFLD.[1]

There are several noninvasive measures used to risk stratify patients with NAFLD. The AASLD guidelines recommend using the NAFLD fibrosis score in patients with NAFLD.[1] (See *The NAFLD fibrosis score*.)

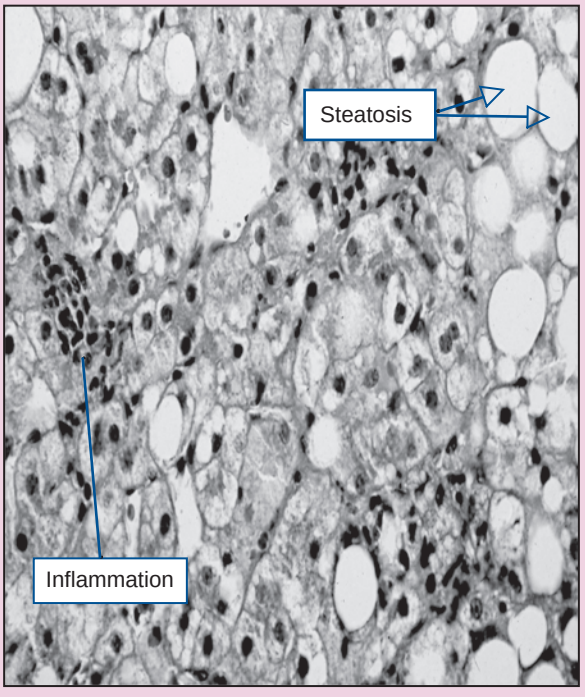
The enhanced liver fibrosis panel measures a set of biomarkers (hyaluronic acid, tissue inhibitor of metalloproteinases-1, and N-terminal propeptide of type III collagen) to predict advanced fibrosis with 80% sensitivity and 90% specificity.[1] Transient elastography has also been studied as a means to risk stratify patients for liver biopsy. Transient elastography measures liver stiffness with a device that utilizes an ultrasound-like probe to send shear waves to the liver and back to the probe.[26,27] It has been shown to have a high degree of accuracy in predicting advanced fibrosis with a 95% sensitivity and 90% specificity.[26-30]

Treatment and management

Treating patients with NAFLD is often an interdisciplinary and collaborative undertaking. Lifestyle modifications that include weight loss through diet and exercise are the mainstay of treating patients with NAFLD.[1,10,31] A 5% to 10% reduction in body weight has been shown to decrease hepatic steatosis and can reduce hepatic inflammation and facilitate regression in fibrosis.[1,10,32] Risk factors for the development of NASH, including metabolic syndrome, should also be addressed, and treatment of these modifiable risk factors should be optimized.[7]

Liver biopsy in a patient with NASH

This liver biopsy sample from a patient with NASH shows steatosis and inflammation.

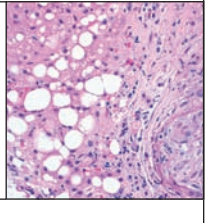


Source: Rhoades RA, Bell DR. *Medical Physiology Principles for Clinical Medicine*. 4th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:548.

The Mediterranean diet has been shown to be beneficial in patients with NAFLD. The diet has been studied in randomized controlled trials against other diets, including diets low in fat and carbohydrates.[33] Patients on the Mediterranean diet experience higher rates of sustained weight loss over time, improvement in insulin sensitivity, and demonstrated a 39% reduction in hepatic steatosis.[33]

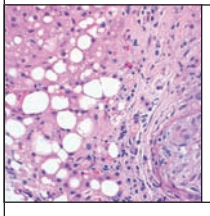
Additionally, a diet rich in high-fructose corn syrup has been shown to increase de novo lipogenesis, which has been linked to the development of both metabolic syndrome and NAFLD.[34] While some studies have shown that a 2 g intake of omega-3 fatty acids has the ability to decrease hepatic steatosis and reduce hypertriglyceridemia,

Lifestyle modifications that include weight loss through diet and exercise are the mainstay of treating patients with NAFLD.



the AASLD does not endorse the use of omega-3s in the treatment of patients with NAFLD alone. However, omega-3s are recommended for use in patients with hypertriglyceridemia and NAFLD.[34]

Another pillar in the treatment of NAFLD is physical activity.[1] Vigorous aerobic activity for as little as 75 minutes per week reduces steatosis in the liver and improves insulin sensitivity in muscle tissue.[34,35] It is hypothesized that aerobic exercise enhances mechanisms of oxidation and export of FFAs from the liver and suppresses the inflammatory state associated with insulin resistance by promoting the release of anti-inflammatory markers from the muscle tissue.[10,34] The greatest success in weight-loss efforts has been shown in patients who combine dietary changes with exercise regimens.[31,32] Research has demonstrated that patients who combine these two lifestyle modifications to achieve greater than 10% total body weight loss have the most dramatic regression of NASH on liver biopsy at 1 year.[32]



Studies showed improvements in hepatic steatosis, inflammation, and fibrosis in patients with NAFLD who had bariatric surgery.

The AASLD treatment guidelines for patients with biopsy-confirmed NASH include the use of high doses of vitamin E in patients without cirrhosis who do not have diabetes mellitus.[1] Randomized controlled studies evaluating the efficacy of vitamin E in patients with NAFLD have demonstrated improvement in LFTs and regression of fibrosis and inflammation on histologic assessment of patients with NASH.[36] However, there are risks of vitamin E therapy. A meta-analysis demonstrated a slight increase in morbidity and mortality in patients taking high-dose vitamin E supplementation.[37]

The AASLD has stated that HMG-CoA reductase inhibitors (statins) can be administered safely in patients with dyslipidemia and NASH, even in the setting of preexisting elevations in LFTs.[1] When used in patients with dyslipidemia and NAFLD, statins have been shown to reduce risks associated with cardiovascular disease and metabolic syndrome.[6] Some studies have demonstrated a reduction of hepatic fibrosis and inflammation in patients with NASH taking lipid-lowering medications.[6,38] The use of statins has been evaluated in patients with NAFLD and elevated LFTs. It has been found that hepatocyte injury does not result from statin use (even in the setting of a minor increase in the LFT elevation) but should be avoided in patients with transaminase levels greater than three times the upper limit of normal.[38]

Bariatric surgery has been shown to play a beneficial role in patients with NAFLD. Although it is not currently a recommended intervention for the treatment of NAFLD, it is not contraindicated in patients who are otherwise eligible for weight-loss surgery.[1] Studies have shown improvements in hepatic steatosis, inflammation, and fibrosis in patients with NAFLD who underwent bariatric surgery.[39,40] Research has found up to 75% of patients with NAFLD who underwent bariatric surgery experienced resolution in steatosis, and 58% of patients experienced some regression of fibrosis.[39,41]

There are currently no FDA-approved pharmacologic interventions for NAFLD, but there are a number of pharmacologic interventions currently under investigation in clinical trials. Obeticholic acid has been shown to reduce hepatic steatosis and fibrosis in both animal models and phase 2b human clinical trials.[6,42,43] Insulin sensitizers are also being evaluated in clinical trials. Elafibranor (GFT505) is an insulin sensitizer that has been shown to have antifibrotic effects on the liver as well as improvements in dyslipidemia, inflammatory markers, and LFTs in both animal models and phase 2b human clinical trials.[44]

Glitazones (in particular pioglitazone) are the most studied pharmacologic compounds in the treatment of NASH. Studies have shown improvements in LFTs, hepatic steatosis, and inflammation but failed to show regression of fibrosis. Long-term effects of pioglitazone are concerning for the development of heart failure, bladder cancer, bone loss, and weight gain that is not always reversible after discontinuing the drug.[1,44] Several new agents are currently under investigation in large, multicenter, randomized controlled trials, including cenicriviroc (an anti-inflammatory agent), aramchol (a metabolic modulator), and GR-MD-02 (an antifibrotic).[44,45]

The NAFLD fibrosis score[1]

The NAFLD fibrosis score is used to risk stratify patients with NAFLD. The score can be calculated from six variables (BMI, age, AST/ALT ratio, platelets, albumin, and blood glucose levels) by using a published formula (http://nafldscore.com). The NAFLD fibrosis score has the ability to predict with 97% specificity and 67% sensitivity which patients will have advanced fibrosis.

A silent disease

With the rise in obesity, the prevalence of NAFLD is increasing and will soon become the leading indicator for liver transplantation. NAFLD is often characterized as a silent disease and is discovered incidentally when patients are being evaluated in the setting of other complaints. Patients can be completely asymptomatic until they reach advanced liver fibrosis and the complications of cirrhosis. NAFLD can be seen on imaging studies decades before fibrosis or abnormal LFTs occur.

Clinicians in all areas of healthcare care for patients with morbidity and mortality secondary to obesity. Additional attention should be given to patients with manifestations of metabolic syndrome, abnormal liver tests, and hepatic steatosis seen on imaging. Prompt referrals to a hepatologist should be made so that patients at greatest risk for disease progression and cirrhosis can be identified. While the mainstay of treatment is currently diet and exercise, FDA-approved pharmacologic therapies will become available in the near future. NP

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