REVIEW

CME CREDIT

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Nonalcoholic fatty liver disease and the epidemic of obesity

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is common in patients with the metabolic syndrome, and it is expected to become more common in countries where obesity, one of the components of the metabolic syndrome, is increasing.

KEY POINTS

NAFLD is a spectrum of disorders that range from simple hepatic steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma.

The most common—and often the only—laboratory abnormalities of patients with NAFLD are mild to moderate elevations of aspartate aminotransferase, alanine aminotransferase, or both.

The diagnosis of NAFLD requires that the patient have no history of significant alcohol intake, no other liver disease, and findings on liver biopsy that are compatible with the disorder.

Biopsy should be reserved for patients at risk of more serious disease, eg, those with persistently elevated liver enzyme levels and other risk factors.

No therapy for NAFLD has been proven effective, but preliminary studies of lipid-lowering agents, insulin-sensitizing agents, antioxidants, and other cytoprotective agents are intriguing.

This paper discusses therapies that are experimental or that are not approved by the US Food and Drug Administration for the use under discussion.

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD), unknown only 2 decades ago, is now ubiquitous, especially among the obese, and the prevalence is expected to increase as our nation gets fatter.[1–8]

We review current thinking about how NAFLD develops, its link with the metabolic syndrome, how to diagnose it, how to decide if a patient needs a liver biopsy, and how to manage it.

A NEWLY RECOGNIZED DISORDER

In 1980, Ludwig et al[9] published the first systematic description of what was then an "unnamed and poorly understood" condition. On liver biopsy, findings resembled those of alcoholic hepatitis, but because the patients did not have a history of heavy drinking, the condition was named "nonalcoholic steatohepatitis."

Nonalcoholic steatohepatitis is now believed to be part of a spectrum of disorders that comprise NAFLD,[1] ie:

- Simple steatosis (fat accumulation within liver cells)
- Steatosis with nonspecific inflammation
- Steatohepatitis (fat accumulation and liver cell injury)
- Cirrhosis (fibrosis, scarring, and nodule formation)
- Hepatocellular carcinoma.

NAFLD IS COMMON

According to radiologic surveys, postmortem studies, and evidence from the third National Health and Nutrition Examination Survey (NHANES III), the prevalence of NAFLD of any type is from 16% to 23% and the preva-

TABLE 1

Factors associated with nonalcoholic fatty liver disease (NAFLD)

- **Metabolic syndrome**
  - Obesity
  - Hypertriglyceridemia
  - Diabetes mellitus
- **Total parenteral nutrition**
- **Lipodystrophy**
- **Wilson disease**
- **Starvation**
- **Jejunoileal bypass**
- **Abetalipoproteinemia**
- **Hypobetalipoproteinemia**
- **Industrial toxins**
- **Weber-Christian syndrome**
- **Medications**
  - Amiodarone
  - Corticosteroids
  - Diltiazem
  - Methotrexate
  - Nifedipine
  - Tamoxifen

From 60% to 95% of patients with NAFLD are obese

lence of steatohepatitis is from 2% to 6%, depending on the diagnostic methods used.[5–7,10–14]

Men and women are equally affected.[15] African Americans appear to have a lower prevalence of NAFLD, although it may simply be underdiagnosed in this group.[16]

NAFLD has also been reported in 2.6% of the general pediatric population,[17] and in 22.5% to 52.8% of children who are obese.[17,18] Some children develop the serious forms of NAFLD, such as cirrhosis.[19,20]

NAFLD AND THE METABOLIC SYNDROME

NAFLD is commonly associated with elements of the metabolic syndrome—obesity, diabetes mellitus, and hypertriglyceridemia.[21–24] From 60% to 95% of patients with NAFLD are obese.[1,25,26] In the morbidly obese, the prevalence of NAFLD is more than 95%, while the prevalence of nonalcoholic steatohepatitis may be as high as 25%.[24] From 21% to 55% of patients with NAFLD have diabetes mellitus, and 20% to 92% have hypertriglyceridemia.[1,2,25–27]

According to data from NHANES III, 21% of men and 27% of women 25 years or older are obese, and 7.3% of adults have diabetes mellitus.[28] Both obesity and diabetes are on the rise in the United States,[28,29] and the prevalence of NAFLD is therefore expected to increase as well.

TABLE 1 lists other conditions associated with NAFLD. Some experts consider NAFLD to be "secondary" when it is associated with conditions other than the metabolic syndrome and "primary" when associated with the metabolic syndrome.[30]

PATHOGENESIS: GENES AND ENVIRONMENT

NAFLD and steatohepatitis probably result from a complex interplay between genes and environment.

A genetic predisposition is suggested by an observed clustering of nonalcoholic steatohepatitis and cryptogenic cirrhosis within families.[31,32] Also suggestive are polymorphisms of genes that encode proteins such as tumor necrosis factor-alpha promoter, microsomal triglyceride transfer protein (involved in the export of triglycerides from the liver), and HFE (involved in hemochromatosis).[33–35]

Multiple 'hits' to steatohepatitis

The "two-hit" hypothesis is the leading theory of the pathogenesis of nonalcoholic steatohepatitis (FIGURE 1).[36]

First hit: Insulin resistance. Insulin resistance is believed to lead to the accumulation of triglycerides in hepatocytes as a result of more fatty acids being synthesized, more free fatty acids being delivered to the liver, less fatty acids being degraded, and less triglycerides being released from the liver.

This link is supported by findings that many patients with NAFLD have hyperinsulinemia, insulin resistance, and the metabolic syndrome,[37–39] even if they do not have diabetes mellitus and are not obese.[37–41] NAFLD has also been reported in patients with severe insulin resistance, such as those with congenital and acquired lipodystrophies.[42,43]

Excessive fat in the hepatocytes may set the stage for the necroinflammation and fibrosis seen in nonalcoholic steatohepatitis.

Second hits: Oxidative stress, cytokines. A variety of second hits could account for the progression from simple steatosis to steatohepatitis.

Oxidative stress occurs when more oxidant substances are produced than the antioxidant processes of the liver can handle. Oxidative stress can cause lipid peroxidation, leading to activation of hepatic stellate cells and hepatocyte death, contributing to hepatocellular injury and fibrosis. Sources of oxidative stress in steatohepatitis include reactive oxidative species that leak from the mitochondria during oxidation of fatty acids; cytochrome P450 enzymes (CYP2E1 and CYP4A); and hepatic iron.[35,44–47]

Cytokine production is increased in nonalcoholic steatohepatitis and is believed to play a role in its pathogenesis. In the liver, tumor necrosis factor-alpha can contribute to oxidative stress[48] and may contribute to insulin resistance through activation of the inhibitor of kappa kinase beta (IKK beta).[49]

Increased free fatty acid levels, in addition to mediating insulin resistance and causing oxidative stress, can be directly hepatotoxic, leading to cellular injury.[15]

Leptin: A possible third hit. Leptin, a protein primarily derived from adipocytes, regulates appetite and energy expenditure.[50,51] It also promotes insulin resistance, contributes both to oxidative stress and to enhanced secretion of inflammatory cytokines,[52–54] and may play a role in causing fibrosis.

Produced by activated hepatic stellate cells, leptin can contribute to fibrosis either directly or indirectly through transforming growth factor-beta-1.[55–57] However, while patients with nonalcoholic steatohepatitis have elevated leptin levels, leptin levels do not correlate with the severity of fibrosis.[52,58]

Although separation of steps involved in the multiple-hit hypothesis of nonalcoholic steatohepatitis provides a convenient scheme, there are probably significant overlaps among these steps. Future research can elucidate the importance of each step in the pathogenesis of this disease.

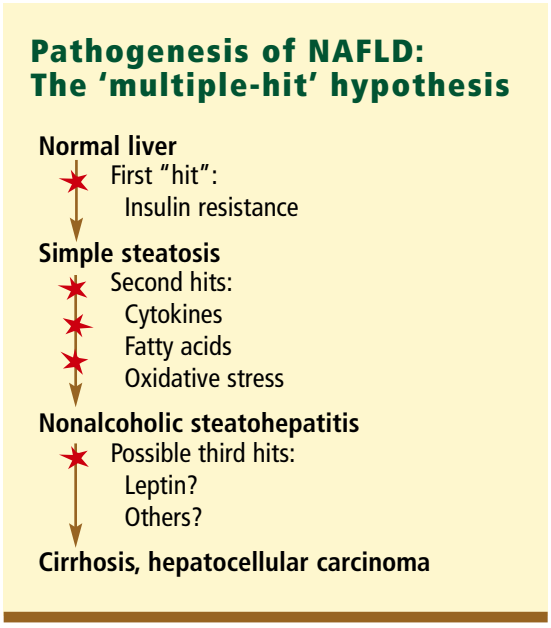

FIGURE 1

CLINICAL FEATURES OF NAFLD

No specific signs or symptoms

Most patients with NAFLD have no specific signs or symptoms, although some complain of fatigue, malaise, and right upper quadrant abdominal pain. Hepatomegaly, found in about half of patients, is sometimes the only physical finding.[26] Jaundice, ascites, gynecomastia, and spider angiomas suggest advanced disease.

About half of patients with NAFLD have hepatomegaly—often the only sign

Mildly elevated AST, ALT

The most common—and often the only—laboratory abnormalities of patients with NAFLD are mild to moderate (twofold to threefold) elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or both.[26] Levels can be as high as 10 to 15 times normal, but this is rare.

In 65% to 90% of patients, the ratio of AST to ALT is less than 1. However, as fibrosis advances, this ratio can reverse and lose its diagnostic value in assessing steatohepatitis.[25]

Other liver enzymes (alkaline phosphatase or gamma-glutamyltransferase) may be elevated two to three times above the normal range.

Hypoalbuminemia, prolonged prothrombin time, and hyperbilirubinemia are less

TABLE 2

How to evaluate suspected NAFLD

Clinical evaluation
- Exclude significant alcohol consumption
- Assess risk factors
  - Obesity
  - Diabetes mellitus
  - Hypertriglyceridemia
  - Insulin resistance syndrome (eg, polycystic ovary syndrome)
- Exclude drugs and other conditions that can cause nonalcoholic fatty liver disease (see TABLE 1)

Laboratory evaluation
- Measure serum levels of:
  - Aspartate aminotransferase (AST)
  - Alanine aminotransferase (ALT)
  - Gamma-glutamyltransferase
- Exclude other causes of liver disease by assessing:
  - Hepatitis B or C serologies
  - Autoimmune markers
  - Ceruloplasmin
  - Alpha-1 antitrypsin level and phenotype
  - Iron studies

Imaging studies
- Ultrasonography, computed tomography, or magnetic resonance imaging for hepatic steatosis (< 33% fat may be normal)

Liver biopsy
- Determine need based on risk (persistently abnormal liver enzymes, obesity, diabetes mellitus, or older age)

common and, when present, suggest advanced disease.

Serum ferritin levels and transferrin saturation may be elevated, but the hepatic iron index and hepatic iron quantitative levels are usually normal.

Imaging can detect NAFLD, but not tell the severity

Ultrasonography is sensitive in detecting steatosis.[59] Noncontrast computed tomography and magnetic resonance imaging can also detect fatty infiltration. However, none of these three imaging methods is especially good for diagnosing steatohepatitis or detecting fibrosis. While all three can detect significant grades of steatosis, none can distinguish between steatohepatitis and the other types of NAFLD.[60]

DIAGNOSIS

A diagnosis of NAFLD or nonalcoholic steatohepatitis requires that:
- The patient have no history of significant alcohol intake (no more than 1–2 drinks per day[15])
- Other liver diseases (especially hepatitis C and Wilson disease) be ruled out (however, NAFLD may coexist with other liver diseases[60])
- The histologic features be compatible with NAFLD.

Biopsy is the definitive test

Because the clinical and laboratory features of NAFLD are not specific and imaging studies cannot reliably distinguish nonalcoholic steatohepatitis from other forms of NAFLD, liver biopsy is the only way to accurately diagnose NAFLD, particularly steatohepatitis. Histologic features include steatosis, lobular inflammation, ballooning degeneration, perisinusoidal fibrosis, and Mallory bodies.[15,61,62]

While pathologists agree that fatty liver disease can be defined as fat accumulation in more than 5% of hepatocytes, there is no consensus regarding steatohepatitis. In general, nonalcoholic steatohepatitis is defined as lobular inflammation and liver cell injury (ie, ballooning degeneration) in association with fat.

Who should undergo liver biopsy?

The role of liver biopsy in routine clinical practice is controversial. Although most experts believe that a biopsy is important for determining both diagnosis and prognosis, few would recommend biopsy for all patients suspected to have NAFLD.[63] Arguments against liver biopsy include its cost and risk, the lack of effective therapy for NAFLD, and NAFLD's generally good prognosis.

Dixon et al[24] found that hypertension, elevated ALT, and insulin resistance predicted steatohepatitis.

Angulo et al[25] found older age, obesity, an AST/ALT ratio greater than 1, and diabetes predicted advanced fibrosis.

We recommend that patients undergo biopsy only if they are at risk of having advanced disease and if liver enzymes remain chronically elevated despite lifestyle changes (TABLE 2).

PROGNOSIS

Data about the natural course of NAFLD are limited. Patients with simple steatosis appear to have a good prognosis, while those with nonalcoholic steatohepatitis may be at risk of their disease progressing to cirrhosis.[1] There is less information on steatosis with nonspecific inflammation.

Simple steatosis is generally benign

Teli et al[3] evaluated 12 patients with simple steatosis diagnosed by biopsy who had a second liver biopsy more than a decade later, and found no histologic evidence that their liver disease had progressed. Despite its limited sample size and relatively short follow-up, this study confirmed the benign nature of simple steatosis.

However, a recent study describes progression of simple steatosis to steatohepatitis in three patients, which is consistent with the multiple-hit hypothesis.[64]

Steatohepatitis is likelier to progress

Matteoni et al[1] histologically categorized 132 cases of NAFLD as either simple steatosis, steatosis with nonspecific inflammation, or steatohepatitis. On follow-up at least a decade later, cirrhosis and liver-related deaths were almost exclusively confined to patients with steatohepatitis.

Few patients with nonalcoholic steatohepatitis have undergone sequential liver biopsies, however. A review of the literature reveals only 30 patients with a documented diagnosis of nonalcoholic steatohepatitis who had sequential liver biopsies over 1 to 9 years.[65] The disease progressed to cirrhosis in about 20% of these patients. A recent study evaluated 22 patients with NAFLD who underwent a second biopsy an average of 5.7 years after the first, and found that 32% had higher fibrosis scores the second time.[64]

Cryptogenic cirrhosis: The end stage of steatohepatitis?

Patients with cirrhosis of unknown origin account for 15% of those waiting for liver transplantation. With sophisticated serologic testing, some of these patients have been reclassified as having viral, autoimmune, or other metabolic liver diseases. However, no clear etiology has been found for many.

Caldwell et al[66] described a cohort of patients with cryptogenic cirrhosis that resembled NAFLD and suggested that cryptogenic cirrhosis may actually be "burned-out" nonalcoholic steatohepatitis. A subsequent case-control study of patients with cryptogenic cirrhosis reported similar findings.[67]

Furthermore, many patients who received liver transplants because of cryptogenic cirrhosis in two case series subsequently developed NAFLD and nonalcoholic steatohepatitis.[68,69] Posttransplant steatohepatitis was associated with the patient profile typical of NAFLD (obesity and type 2 diabetes mellitus).

Hepatocellular carcinoma part of spectrum

Patients with hepatocellular carcinoma and cryptogenic cirrhosis also have clinical profiles similar to those of patients with NAFLD, suggesting that carcinoma may also be a part of this liver disease spectrum.[70] These data also suggest that nonalcoholic steatohepatitis may be an important cause of cryptogenic cirrhosis and hepatocellular carcinoma.[68]

Steatohepatitis may progress to cirrhosis, but data are scarce

TREATMENT: MANAGE ASSOCIATED CONDITIONS

There currently is no proven effective therapy for nonalcoholic steatohepatitis. Early efforts focused on modifying the associated conditions such as obesity, hypertriglyceridemia, and diabetes mellitus. More recent efforts have targeted theoretical aspects of the pathogenesis, such as insulin resistance and oxidative stress.

Weight loss, particularly of 10% or more, can lead to improvements in liver enzyme abnormalities[71] and in hepatic steatosis as observed on ultrasonography.[72]

There has been, however, very little histologic follow-up in obese patients who lost weight. In 1986, Eriksson et al[73] reported that two patients with nonalcoholic steatohepatitis who lost weight had significant histologic improvement on follow-up liver biopsies. Ueno et al[74] also reported significant improvement on serial biopsies in patients who lost weight.[74]

Very rapid weight loss, however, may lead to increased portal inflammation and fibrosis.[75,76] While the optimum rate of weight loss is not clear, gradual loss of 10% of baseline weight seems to be a reasonable recommendation.[77]

Lipid-lowering agents have been evaluated in patients with nonalcoholic steatohepatitis. Patients did not appear to benefit from 12 months of clofibrate.[78] On the other hand, atorvastatin for 1 year produced significant improvement in ballooning degeneration and inflammatory scores in seven patients.[79] A randomized controlled trial of short-term gemfibrozil in 46 patients demonstrated a significant decrease in serum aminotransferase levels, but histologic data were unavailable.[80]

Ursodeoxycholic acid may help patients with nonalcoholic steatohepatitis. Improvements in serum aminotransferase levels and in steatosis occurred in small-scale pilot studies.[78,81,82] However, a recent trial found no biochemical or histologic improvement in patients treated with low-dose ursodeoxycholic acid compared with placebo.[83]

Increase insulin sensitivity

Gradual loss of 10% of weight seems to be reasonable to control NAFLD

Blood sugar levels of patients with NAFLD should be controlled. Agents that improve insulin sensitivity have been tested.

Metformin 500 mg three times a day for 4 months was given to 14 patients with NAFLD in a pilot study.[84] Their serum aminotransferase levels declined significantly. Histologic follow-up was not available.

Thiazolidinediones. Troglitazone, rosiglitazone, and pioglitazone are antidiabetic agents that improve insulin sensitivity.

Troglitazone was given for 6 months to 10 patients who had biopsy-proven nonalcoholic steatohepatitis.[85] Serum aminotransferase levels normalized in seven patients by the end of the treatment period, but histology on follow-up liver biopsies did not significantly improve. Troglitazone has now been withdrawn from the market because of hepatotoxicity.

Rosiglitazone was given to a larger number of patients for 12 months, with biochemical and histologic improvement.[86] Similar results were noted in a separate study with pioglitazone.[87]

While the results of these studies are promising and warrant further evaluation, the thiazolidinediones are potentially hepatotoxic, and their use in NAFLD should be restricted to clinical trials at this time.

Antioxidants and other cytoprotective agents

Vitamin E may improve nonalcoholic steatohepatitis because it protects cellular structures against damage from oxygen free radicals and reactive products of lipid peroxidation.

In a pilot study, 11 obese children with NAFLD all showed normalization of their liver enzyme levels after taking vitamin E 400 to 1,200 IU/day.[88]

In another study, 12 patients with nonalcoholic steatohepatitis and 10 with simple steatosis took vitamin E 300 IU/day for 12 months.[89] Liver enzyme levels declined significantly. Inflammation and fibrosis also improved in 6 of 9 patients with nonalcoholic steatohepatitis who underwent liver biopsy at the end of the treatment period.

Betaine, a metabolite of choline that increases S-adenosylmethionine levels, reduced serum aminotransferase levels and improved histologic findings in 10 patients with nonalcoholic steatohepatitis.[90]

N-acetylcysteine given for 3 months resulted in biochemical improvement in patients with nonalcoholic steatohepatitis in a small study.[91]

CONTROLLED STUDIES NEEDED

Preliminary studies have generated intriguing results, but randomized, placebo-controlled clinical trials that target specific pathogenic mechanisms would be preferable. This will not be possible until the pathogenesis of nonalcoholic steatohepatitis is better understood. Advances in clinical investigative methods, laboratory medicine, functional genomics, and pharmacogenomics will further this effort.

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