Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) comprises a spectrum of conditions, ranging from steatosis without inflammation to steatohepatitis with inflammation, fibrosis, and even cirrhosis. Originally termed *nonalcoholic steatohepatitis* (NASH) by Ludwig and colleagues,[1] this increasingly recognized disorder has more recently been termed NAFLD to encompass both steatosis and NASH. Although NASH was first described more than 20 years ago, reports of its natural history have only recently been published.

Certain groups of persons are recognized as having an increased prevalence of NAFLD, in particular those with obesity or diabetes mellitus. There is, however, less information available about the pathogenesis and treatment of this disorder than about its epidemiology. Because of the concomitant diagnoses associated with NAFLD, therapy typically has included weight reduction and administration of lipid-lowering agents and antioxidants. Treatment of these associated disorders and of insulin resistance can lead to clinical improvement in severity of steatosis, serum aminotransferase levels, and—potentially—hepatic inflammation and fibrosis.

This article provides an overview of NAFLD, focusing on its definition, epidemiology, pathogenesis, clinical features, laboratory and radiographic findings, and treatment. The need for larger studies with longer follow-up is stressed.

DEFINITION

NAFLD describes the condition of persons who have steatosis and steatohepatitis, with or without significant fibrosis or cirrhosis. Most studies have evaluated patients with NASH only. Ludwig and colleagues originally described 20 patients over a 10-year period who had findings suggestive of alcoholic hepatitis on liver biopsy (ie, steatosis with lobular inflammation) but no history of significant alcohol consumption.[1] The majority of these patients were female (60%), and 90% were obese. Approximately 25% of them had hyperlipidemia or diabetes mellitus. Many of the patients also had hepatomegaly and elevated serum levels of aminotransferases. Findings on liver biopsy included macrovesicular steatosis, lobular inflammation, and Mallory bodies. Cirrhosis was present in 15% of biopsies obtained. These pathologic findings are identical to findings seen in patients with alcoholic steatohepatitis; the distinction between alcoholic and nonalcoholic forms of steatohepatitis is based on patient history.

Powell and colleagues[2] suggested the following 3 diagnostic criteria for NASH: (1) liver biopsy results showing moderate to gross macrovesicular fatty degeneration with inflammation, with or without Mallory bodies, fibrosis, or cirrhosis; (2) consumption of less than 40 grams of alcohol per week; and (3) the absence of other liver disease (eg, hepatitis B or C).

EPIDEMIOLOGY

In many published series, NAFLD has been most prevalent in women age 40 to 60 years. Recent reports, however, emphasize an appreciable prevalence in male patients. The estimated overall prevalence of NAFLD varies among reports, ranging from 6% to 40%.[3,4] This wide range in prevalence most likely reflects differences in the definitions used and patient populations studied. Some studies reporting on prevalence of NAFLD may include patients with steatosis, whereas others may include only persons with steatohepatitis. Moreover, the generally reported rates from referral centers may not reflect the actual prevalence in the general population.

A higher prevalence of fatty liver disease is seen in studies of patients with diabetes mellitus or obesity and in studies that include steatosis as part of the definition of liver disease. Lower rates are seen in studies of the general population and in studies in which steatohepatitis is the only liver disorder described. In patients undergoing liver biopsy because of elevated serum aminotransferase levels, NASH was seen in 7% to 11% of cases.[1,5] In studies of patients with diabetes mellitus and of obese patients

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Table 1. Risk Factors for NAFLD

Diabetes mellitus
Drugs
Amiodarone
Corticosteroids
Isoniazid
Tamoxifen
Female gender
Hyperlipidemia
Jejunoileal bypass
Obesity
Total parenteral nutrition

NAFLD = nonalcoholic fatty liver disease.

with elevated serum aminotransferase levels, steatohepatitis was seen in 18% to 36% of cases.[6,7] NAFLD also has been described in patients who have undergone surgery to treat their obesity or have been treated with total parenteral nutrition and particular medications. **Table 1** lists risk factors associated with NAFLD.

ASSOCIATED CONDITIONS

As previously indicated, obesity, diabetes mellitus, and hyperlipidemia are all associated with NAFLD (**Table 2**). Studies have shown an increased prevalence of these conditions in patients with steatosis or steatohepatitis. For example, the rate of obesity in subjects with NAFLD has been reported to be from 30% to 98%.[2,8,9] Diabetes mellitus or hyperglycemia is seen in 21% to 33% of patients with NAFLD, and hyperlipidemia is seen in 21% to 60%.[2,9,10] Typically, serum triglyceride or cholesterol levels are elevated. It appears that NAFLD, diabetes mellitus, and hyperlipidemia share a similar pathogenesis. It is likely that steatohepatitis is mediated through insulin resistance, a common factor in all of these conditions.

NATURAL HISTORY

Studies of the natural history of NAFLD suggest that most affected persons do not develop cirrhosis.[2,8,10,11] However these studies are limited by their small sample size and short follow-up time (**Table 3**). As evident in studies of hepatitis C, patients with chronic hepatitis may not develop cirrhosis for 20 to 30 years after disease onset.[12] In the description by Ludwig and colleagues, 15% of 20 liver biopsies from patients with NASH showed cirrhosis.[1] Yet, in 39 patients followed for approximately 4 years, most of whom were middle-aged, obese women, only 1 patient died of liver disease.[11] Repeat liver biopsy specimens from 5 of 13 patients showed progression of fibrosis, with 2 of these patients developing cirrhosis. The remaining 8 patients had no increase in fibrosis.

Table 2. Disorders Associated with NAFLD

Disorder	Prevalence in Patients with NAFLD
Obesity	30%–98%
Hyperlipidemia	21%–60%
Increased serum iron levels	58%
Diabetes mellitus	21%–33%

Data from Wanless and Lentz,[3] Silverman et al,[4] Matteoni et al,[8] and Bacon et al.[9]

NAFLD = nonalcoholic fatty liver disease.

Table 3. Summary of Studies of NAFLD and Cirrhosis

Source	Number of Patients	Follow-up Period	Patients with Cirrhosis
Lee[11]	39 (13 with serial biopsies)	3.5 y	2 of the 13 (15%)
Powell et al[2]	42	4.5 y	3 (7%)
Bacon et al[9]	33	None	5 (15%)
Teli et al[10]	40 (12 with serial biopsies)	11 y	0
Matteoni et al[8]	132	None	(4%–26%)

NAFLD = nonalcoholic fatty liver disease.

A subsequent study of 42 patients with NASH followed subjects for a median of 4.5 years.[2] All but 2 of these patients were obese; 83% were female, 81% were hyperlipidemic, and 36% were hyperglycemic. At initial presentation, 18 of these patients had fibrosis, and 1 had cirrhosis. During follow-up, the patient with cirrhosis died of hepatocellular carcinoma, and 3 patients progressed to cirrhosis.

Teli and colleagues followed 40 patients for a median of 11 years.[10] Twelve patients were obese, 4 had diabetes mellitus, and 9 had hyperlipidemia. None of the patients in the study developed cirrhosis; 12 (48%) had repeat liver biopsies and elevated levels of liver enzymes. One person developed mild fibrosis after 10 years. Another study showed that the rate of cirrhosis is 6-fold higher if findings of inflammation or fibrosis are characterized by ballooning degeneration or Mallory bodies.[8] If steatosis is the only finding on liver biopsy, then fibrosis is uncommon.

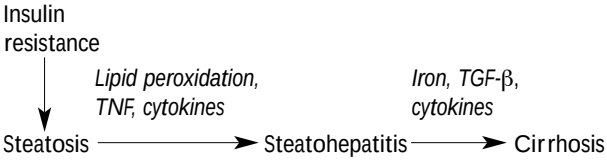

Figure 1. Pathogenesis of nonalcoholic fatty liver disease. TGF = tumor growth factor; TNF = tumor necrosis factor.

The above data suggest that a minority of persons with NAFLD develop cirrhosis and that it is rare for steatosis alone to lead to fibrosis. It appears that if inflammation accompanies steatosis, there is a greater risk of fibrosis and cirrhosis. However, the development of cirrhosis may take decades, and the usual follow-up of published studies is only 10 years or less, with relatively few patients. Data from studies following a greater number of patients for longer periods of time are needed before the risk for cirrhosis associated with NAFLD is truly understood.

PATHOGENESIS

The pathogenesis of steatosis and steatohepatitis is poorly defined but, as suggested earlier, may be mediated by insulin resistance. The strong association between NAFLD and conditions associated with syndrome X (eg, diabetes mellitus, hyperlipidemia, obesity) support insulin resistance as a pathogenic mechanism of NAFLD. Steatosis occurs because the liver metabolizes free fatty acids, which are partly mediated by lipase. Lipase is inhibited by insulin, and persons with insulin resistance have elevated serum insulin levels. When free fatty acids accumulate in the liver, they are oxidized by mitochondria and used for the formation of triglycerides and cholesterol. If the delivery of free fatty acids exceeds the capacity of mitochondrial oxidation, then triglycerides and fat accumulate in the liver.[13] Bacterial overgrowth and endotoxin production may contribute to hepatic steatosis, which is the proposed mechanism in patients who have undergone jejunoileal bypass.

The mechanism leading from steatosis to steatohepatitis is not known. Oxidative stress and lipid peroxidation may play a role in the development of inflammation. Hepatic cytochrome P-450 expression is increased in patients with NAFLD.[13,14] Increased expression of this enzyme can lead to increased lipid peroxidation, resulting in increased oxidative stress and inflammation. Cytokine expression may result from free radicals being released as a result of lipid peroxidation. Increased hepatic expression of tumor necrosis factor may be found.[13] Moreover, serum levels of ferritin and iron may be elevated in persons with NAFLD; iron can activate stellate cells, which produce collagen.[13,15] **Figure 1** summarizes some of the potential mechanisms leading from steatosis to steatohepatitis and cirrhosis.

DIAGNOSIS

Clinical Findings and Laboratory Studies

Most persons with NAFLD are asymptomatic, and their condition is diagnosed only after screening blood work reveals elevated serum aminotransferase levels. In patients who are symptomatic, the most common symptoms are right-upper-quadrant pain and fatigue.[5] Affected patients may have hepatomegaly on physical examination, but stigmata of portal hypertension or advanced liver disease are uncommon.

Laboratory studies typically reveal a serum alanine aminotransferase (ALT):aspartate aminotransferase (AST) ratio greater than 1 (in contrast to alcoholic hepatitis, in which AST is the predominantly elevated enzyme). Prothrombin time and serum bilirubin level are usually within normal limits. γ-Glutamyltransferase (GGT) is a sensitive marker for fatty liver but is not specific. Occasionally, patients with NAFLD may have elevations in GGT and alkaline phosphatase levels but normal serum aminotransferase levels.

Iron levels (in particular, ferritin) may be elevated, but no convincing association between NAFLD and hemochromatosis has been demonstrated.[9,16] Hepatic iron level is elevated in male patients with NAFLD but not to levels seen with hemochromatosis. The effect of the hemochromatosis mutation on fibrosis in patients with NAFLD is controversial,[16] with studies arguing both for and against an association between heterozygosity of the C282Y mutation and increased severity of liver disease in patients with NAFLD.

As indicated previously, studies suggest that female sex is associated with NAFLD.[5] However, not all studies have shown that a majority of persons with the disorder are female, are obese, or have diabetes mellitus. In a study of 33 subjects with NAFLD, 58% were men, 61% were not obese, and 79% had normal glucose and lipid levels.[9] In addition, liver biopsy showed cirrhosis in 5 patients. Thus, although the majority of studies point to an association between NAFLD and certain risk factors, the diagnosis should be considered in persons who have elevated levels of liver enzymes but no other associated risk factors.

Radiologic Studies

Ultrasonography of the abdomen in patients with NAFLD may reveal an echogenic pattern suggestive of

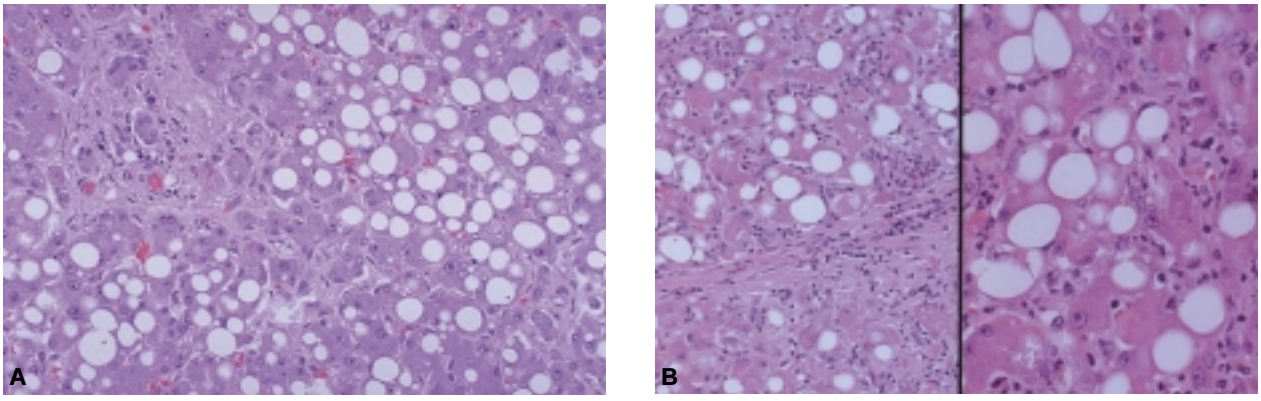

Figure 2. Photomicrographs of liver biopsy specimens. (**A**) Photomicrograph showing steatohepatitis. (**B**) High-power photomicrograph showing inflammatory cells (left) and fibrosis (right).

fatty infiltration. Although this finding may provide further evidence in support of a diagnosis of NAFLD, ultrasonography is not diagnostic of the disorder. Ultrasonography has a sensitivity of 82% to 90% for detecting a fatty liver, and the sensitivity approaches 100% when steatosis involves more than 10% of the liver on biopsy.[17,18] When ultrasonography shows an echogenic pattern of the liver, the specificity for steatosis is 93%.[18] Although fibrosis and inflammation may result in a typical ultrasonographic pattern,[18] this finding does not reliably distinguish fat from fibrosis or reliably diagnose cirrhosis.[19] Hepatic inflammation, fibrosis, and cirrhosis are most accurately diagnosed by liver biopsy results. Standard computed tomographic (CT) techniques do not add any more information about fatty liver disease than is available through ultrasonography. Specialized CT and magnetic resonance imaging techniques are under investigation to determine if they can provide noninvasive methods of determining the amount of hepatic inflammation and fibrosis that are present.[20]

Patients with elevated liver enzyme levels and risk factors for NAFLD should undergo abdominal ultrasonography to discover any echogenic pattern in the liver, which would suggest fatty infiltration. If other causes of chronic liver disease are excluded, the diagnosis of NAFLD can be presumed on the basis of history, physical examination findings, laboratory data, and ultrasonographic findings. The role of liver biopsy in grading the degree of inflammation and staging the degree of fibrosis can then be discussed with the patient.

Liver Biopsy and Noninvasive Measures

The role of liver biopsy in diagnosing NAFLD is controversial. Liver biopsy is not typically needed to establish the diagnosis, and biopsy results infrequently change the presumptive diagnosis.[21] Liver biopsy is helpful in establishing the degree of inflammation and fibrosis (**Figure 2**). In a previously cited study of 132 patients with NAFLD, 49 had steatosis only, 10 had steatosis with lobular inflammation, 19 had steatosis with ballooning degeneration, and 54 had steatosis with ballooning degeneration and Mallory bodies or fibrosis on biopsy.[8] Typical findings on liver biopsy of patients with NAFLD are listed in **Table 4**. In our practice, we discuss performing liver biopsy with most of our patients who have NAFLD and elevated liver enzyme levels. Patients who have significant fibrosis are considered for treatment protocols, because there is no established therapy for this condition.

Table 4. Findings on Liver Biopsy in Patients with NAFLD*

Macrovesicular steatosis
Lobular inflammation
Hepatocyte necrosis
Ballooning degeneration
Mallory bodies
Hepatic iron
Fibrosis
Cirrhosis

NAFLD = nonalcoholic fatty liver disease.

*Entries are arranged in order of decreasing frequency.

Investigators have evaluated various noninvasive measures of inflammation and fibrosis. For example, in a study of 144 subjects with biopsy-established NASH, 74% of whom had fibrosis or cirrhosis, predictors of significant fibrosis included age, obesity, diabetes mellitus, and an AST:ALT ratio greater than 1.[22] Similarly, body

Table 5. Potential Treatments of NAFLD

Nonpharmacologic therapy
Diet
Exercise
Pharmacologic therapy
Betaine
Cholesterol-lowering agents
Metformin
Thiazolidinediones
Ursodeoxycholic acid
Vitamin E

NAFLD = nonalcoholic fatty liver disease.

mass index is associated with the degree of steatosis. A study of 105 patients undergoing laparoscopic surgery to treat their obesity reported that insulin resistance, hypertension, and an elevated ALT level were associated with inflammation and fibrosis.[23] A score developed from these predictors had a sensitivity of 80% and a specificity of 90% for NASH. Although noninvasive determinants of inflammation and fibrosis may be helpful in patients with NAFLD, they are currently limited in their ability to detect inflammation and fibrosis.

TREATMENT

There is no established therapy for NAFLD. Because many affected patients have diabetes mellitus, coronary artery disease, or obesity, diet and exercise—with or without administration of lipid-lowering agents—are typically recommended (**Table 5**). The effect of diet, use of lipid-lowering agents, and oral administration of hypoglycemic agents has been evaluated.[24–26] In 48 patients with either diabetes mellitus, hyperglycemia, or hyperlipidemia, a regimen of diet, lipid-lowering agents, and oral administration of hypoglycemic agents resulted in weight reduction and improvement in lipid profile. Moreover, almost every patient had a decrease in serum aminotransferase levels. However, follow-up liver biopsies were not performed, so the effect of these interventions on histology was not determined. In general, weight reduction should not be too rapid, because rapid weight loss is associated with steatohepatitis.[27] Patients also should be advised to abstain from alcohol completely or to consume it only rarely.

Administration of ursodeoxycholic acid and clofibrate was evaluated in a nonrandomized clinical trial of 40 patients with NASH.[28] Of these patients, 63% of were women, and 40% had hypertriglyceridemia. Their mean weight was 90 kg (198 lb). Sixteen patients with hypertriglyceridemia were treated with clofibrate and 24 were treated with ursodeoxycholic acid for 1 year. A liver biopsy was performed prior to entry into the study and after 1 year of therapy. There was no significant effect on serum aminotransferase levels, severity of hepatic steatosis, inflammation, or fibrosis in the group receiving clofibrate. However, the group receiving ursodeoxycholic acid had a reduction in alkaline phosphatase, ALT, and GGT levels and in severity of steatosis. Larger studies of ursodeoxycholic acid are warranted, based on the promising results from this study.

Other therapies for NAFLD have been evaluated, including administration of vitamin E, betaine, and metformin. A study of 11 children with NASH, diagnosed on the basis of an elevated serum ALT level and an echogenic liver on ultrasonography, showed a reduction of serum ALT level during vitamin E therapy (dose, 400 to 1200 IU/day).[29] The mean serum ALT level decreased from 175 IU/L to 40 IU/L. Interestingly, serum ALT levels increased after vitamin E was discontinued. Because liver biopsy was not performed, the effect on histology could not be determined. In another study, 10 patients with NASH received a 1-year course of betaine (a metabolite of choline)[30]; 7 patients completed the study. By the end of the year, 3 of the 7 had normal serum aminotransferase levels, and another 3 had a 50% decline in these levels. Diminishment of liver inflammation or fibrosis also was seen in approximately half of the patients. Finally, in an animal model of NAFLD, metformin reversed hepatic steatosis in leptin-deficient mice.[31] The authors speculated that metformin decreased hepatic expression of tumor necrosis factor, reducing hepatic lipid accumulation.

Many patients with NAFLD have hypercholesterolemia, as well as elevated serum aminotransferase levels. Many physicians are concerned about administering lipid-lowering agents to these patients, because most of these medications can elevate serum aminotransferase levels. However, many patients with NAFLD have risk factors for coronary artery disease (eg, diabetes mellitus, elevated serum cholesterol level), so the benefits they would derive from lowering their cholesterol level most likely outweigh the theoretical risk of liver injury. Thus, lipid-lowering agents should be administered to patients with NAFLD when indicated, with careful monitoring of liver function test results while they are on therapy.

CONCLUSION

NAFLD is an increasingly recognized disorder, with findings ranging from steatosis, to steatohepatitis, to

cirrhosis. Studies evaluating the natural history of NAFLD suggest that most patients with the disorder do not develop cirrhosis, but larger studies with longer follow-up are needed to determine all the potential effects of NAFLD. As shown in cases of chronic hepatitis C and other causes of chronic liver disease, it may take decades for cirrhosis to develop. Perhaps serum collected decades ago from persons with elevated serum aminotransferase levels and risk factors for NAFLD but no known underlying liver disease could provide needed data.

Many persons with NAFLD have conditions associated with insulin resistance, such as obesity and diabetes, suggesting that insulin resistance is a key factor in the pathogenesis of the disorder. Steps progressing from steatosis to steatohepatitis and cirrhosis are unclear but may involve lipid peroxidation and hepatic expression of cytokines, leading to fibrinogenesis. Treatment is aimed at improving insulin resistance, reducing hepatic oxidative stress, and decreasing the cytokine expression that promotes inflammation and fibrosis. Weight loss in overweight patients, optimal management of diabetes mellitus, and avoidance of alcohol are all indicated. Vitamin E and ursodeoxycholic acid are often used to treat steatohepatitis, but long-term studies of these and other interventions (eg, metformin) are awaited. Future studies on treatment should focus on patients who have fibrosis and should correlate the effects of intervention on hepatic fibrosis and inflammation. Because data suggest that few patients with NAFLD develop cirrhosis, the identification of risk factors associated with fibrosis should improve selection of NAFLD patients who warrant therapy. **HP**

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