

SPECIAL REPORTS AND REVIEWS

Nonalcoholic Steatohepatitis

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Nonalcoholic steatohepatitis (NASH) is a condition characterized by hepatomegaly, elevated serum aminotransferase levels, and a histologic picture similar to alcoholic hepatitis in the absence of alcohol abuse. Most patients with NASH are obese women, and many have diabetes mellitus, hypercholesterolemia, or hypertriglyceridemia. NASH has also been associated with a number of metabolic conditions, surgical procedures, and drug treatments. Most patients are asymptomatic. The most common sign of NASH is hepatomegaly. Stigmata of chronic liver disease are rare. Laboratory abnormalities include a 2–4-fold elevation of serum aminotransferase levels; other liver function test results are usually normal. Histologically, there is moderate to severe macrovesicular steatosis and lobular hepatitis with necrosis or ballooning degeneration and/or fibrosis. The pathogenesis of NASH is poorly understood, but lipid peroxidation and oxidative stress are the leading culprits. The natural history of NASH is unknown, but NASH seems to be a stable disease in most patients. Treatment of NASH is unproven, but weight reduction is recommended in obese patients. Small pilot studies of several drugs have shown promise, but large randomized clinical trials are awaited. Orthotopic liver transplantation is the treatment of choice for end-stage liver disease secondary to NASH.

In 1980, Ludwig et al.¹ coined the term nonalcoholic steatohepatitis (NASH) to describe the morphologic pattern of liver injury in 20 patients evaluated at the Mayo Clinic over a 10-year period. These patients had histologic evidence of alcoholic hepatitis on liver biopsy but no history of alcohol abuse. No cause of liver disease could be identified. Sixty percent of the patients in this original series were women, with a mean age of 54 years. Ninety percent were obese (>110% of ideal body weight), and 25% had a history of hyperlipoproteinemia, adult-onset diabetes mellitus, or both. Most patients were evaluated for abnormal liver function test results and were asymptomatic. On physical examination, hepatomegaly was present in 75% of patients, splenomegaly in 25%, and ascites and spider angiomas in 5%. Elevated serum aminotransferase levels were present in 90%

of these patients, and the rest of the liver profile was near normal or normal. Hyperglycemia was present in 50%, hypertriglyceridemia in 76%, and hypercholesterolemia in 36%. On liver biopsy, the hallmark features were moderate to severe macrovesicular steatosis with lobular inflammation. Mallory bodies were found in 70% of specimens. Perisinusoidal, centrilobular, and/or septal fibrosis was present in 70%, and cirrhosis was evident in 15% of specimens. Based on the review of these 20 patients, Ludwig et al.¹ proposed a classification scheme for steatohepatitis that recognized the existence of a previously undescribed entity, NASH, that was histologically identical to alcoholic hepatitis but had a different epidemiologic and clinical profile. Much has been learned about the epidemiology, pathogenesis, and prognosis of NASH since the initial description of the disorder. It is clear that although NASH is an indolent disease with little clinical sequelae in most patients, it can evolve into cirrhosis and hepatic failure requiring liver transplantation. The purpose of this review is to elucidate what is known about NASH and to provide a rational approach for diagnosis and management of this disease.

Epidemiology of NASH

NASH has been reported worldwide, although geographic variations in prevalence are evident. NASH is the histologic diagnosis in 7%–11% of patients undergoing liver biopsy in the United States and Canada^{1,2} but is found in only 1.2% of patients undergoing liver biopsy in Japan.³ In a recent histologic study, NASH was documented in 26% of 81 nonalcoholic patients with

Abbreviations used in this paper: BMI, body mass index; CYP2E1, cytochrome P450 2E1; HCV, hepatitis C virus; HIC, hepatic iron concentration; IL, interleukin; IRS, insulin resistance syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PDGF, platelet-derived growth factor; PT, prothrombin time; TGF, transforming growth factor; TNF, tumor necrosis factor; UDCA, ursodeoxycholic acid.

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Table 1. Important Epidemiologic Features of NASH

Female sex	60%–83%
Obesity	40%–100%
Type II diabetes mellitus, hyperglycemia, or glucose intolerance	20%–75%
Hyperlipidemia	20%–81%

marker-negative abnormal liver function test results.⁴ NASH may be even more prevalent among asymptomatic patients with elevated liver function test results, negative viral markers, and negligible alcohol intake because many of these patients do not undergo liver biopsy. The prevalence of NASH in the general population has not been defined. In a large autopsy series of 351 unselected nonalcoholic obese and nonobese patients, the prevalence of NASH was 6.3%.⁵ NASH has been described in obese adolescents^{6,7} as well as adults. Most cases occur in persons in the fourth to sixth decades of life.^{1,8–10} Women are 60%–83% of patients with NASH in most clinical studies^{1,9,11–13}; however, recent studies suggest that men may be afflicted equally.^{8,14–16}

The most important epidemiologic features of NASH are listed in Table 1. Obesity is the condition most often reported in association with NASH. The earliest report of “fatty liver hepatitis,” an early name for what was later called NASH, was in a cohort of obese patients.¹⁷ Subsequent studies have consistently shown a strong association between obesity and NASH. Obesity is described in 40%–100% of patients with NASH, depending on the definition of obesity that is used.^{1,8,10,12,15,16} In a study of 100 morbidly obese patients undergoing gastric bypass surgery, 36% had some degree of steatohepatitis.¹⁸ Other studies have documented NASH in 9%–26% of obese patients.^{19,20} The prevalence of NASH seems to correlate with the degree of obesity. In the autopsy series by Wanless and Lentz,⁵ NASH was found in 2.7% of lean patients (<110% of ideal body weight) and 18.5% of markedly obese patients (>140% of ideal body weight). In this study, the degree of obesity correlated positively with the prevalence and severity of steatosis, and the prevalence of NASH was proportional to the severity of steatosis. This correlation between body mass index (BMI), steatosis, and NASH has been demonstrated in several studies,^{9,21} but other studies have failed to show such an association.^{11,12} The distribution of body fat may be more important in the development of hepatic steatosis than the total adipose mass. One study has shown a significant correlation between the degree of hepatic steatosis and the waist-to-hip ratio,²² pointing to the importance of intra-abdominal or visceral fat as a predictor of fatty liver,²³ which is a precursor of NASH.^{22–24}

NASH has been associated with type 2 diabetes mellitus and glucose intolerance, with or without superimposed obesity. Type 2 diabetes, hyperglycemia, and glucose intolerance have been described in 20%–75% of adult patients with NASH.^{1,8–12,16} Wanless and Lentz⁵ reported that a history of type 2 diabetes was associated with a 2.6-fold increase in the prevalence of NASH. The association between type 2 diabetes and NASH was greatest in morbidly obese patients. The investigators also observed a statistically insignificant trend toward increased prevalence of NASH among patients with type 2 diabetes requiring insulin therapy compared with diabetic patients not receiving insulin. The spectrum of nonalcoholic fatty liver disease (NAFLD), including NASH, has been associated with insulin resistance and hyperinsulinemia,^{21,25} even in lean subjects with normal glucose tolerance.²⁵ These findings suggest that insulin resistance, which often occurs in conjunction with other metabolic derangements as part of the insulin resistance syndrome (IRS), may be a primary phenomenon in the development of hepatic steatosis and NASH.

Hyperlipidemia is found in a large proportion of patients with NASH. In published series, hypertriglyceridemia, hypercholesterolemia, or both were present in 20%–81% of patients with NASH.^{1,8,9,12,15,16,25,26} Most patients with NASH have multiple risk factors, includ-

Table 2. Conditions Associated With NASH

Acquired metabolic conditions
Obesity
Diabetes mellitus
Hyperlipidemia
Rapid weight loss
Total parenteral nutrition
Acute starvation
Inborn errors of metabolism
Wilson disease
Abetalipoproteinemia
Tyrosinemia
Hypobetalipoproteinemia
Surgical procedures
Jejunioileal bypass
Biliopancreatic diversion
Extensive small bowel resection
Gastroplasty for morbid obesity
Drugs/toxins
Amiodarone
Glucocorticoids
Perhexiline maleate
Synthetic estrogens
Tamoxifen
4,4'-diethylaminoethoxyhexestrol
Isoniazid
Industrial exposure to petrochemicals
Miscellaneous factors
Partial lipodystrophy
Jejunal diverticulosis with bacterial overgrowth

ing obesity, type 2 diabetes, and hyperlipidemia. However, Bacon et al.⁸ reported that 14 of 33 patients in their series had none of these risk factors. This finding may reflect selection or referral bias, or may signal a true expansion in the demographic and clinical profile of NASH.

Other metabolic, surgical, and genetic conditions are also associated with NASH. Jejunoileal bypass, once a popular treatment for morbid obesity, was associated with a 40% incidence of liver function abnormalities postoperatively and with severe NASH and hepatocellular failure in up to 6% of patients.^{27,28} NASH has also been described after biliopancreatic diversion,²⁹ extensive small bowel resection,³⁰ gastroplasty for morbid obesity,³¹ and prolonged total parenteral nutrition.^{32,33} NASH has been associated with limb lipodystrophy,³⁴ Weber-Christian disease,³⁵ small intestinal diverticulosis with bacterial overgrowth,³⁶ abetalipoproteinemia,³⁷ and therapy with 4,4'-diethylaminoethoxyhexestrol,³⁸ amiodarone,³⁹ perhexiline-maleate,⁴⁰ tamoxifen,⁴¹⁻⁴³ isoniazid,⁴⁴ and synthetic steroids.⁴⁵ NASH has been described recently as a consequence of chronic exposure to petrochemical substances in the workplace.⁴⁶ The conditions associated with NASH are summarized in Table 2.

Clinical and Laboratory Features

The clinical and laboratory features of NASH are summarized in Table 3. NASH is asymptomatic in a large proportion (48%–100%) of patients.^{8,12,47-50} Symptoms that have been described include vague right upper quadrant pain, fatigue, and malaise. These symptoms may be more prominent in adolescents with NASH.^{6,7} NASH is often discovered incidentally during evaluation for an unrelated medical condition.^{1,12} Most patients with NASH have elevated liver function test results and/or hepatomegaly.^{1,8,12,47} Hepatomegaly has been described in up to 75% of patients with NASH,^{1,12,47} although it is often difficult to appreciate on physical examination.

Stigmata of chronic liver disease are rare,^{1,9,12,47,51} although splenomegaly was noted at the time of diagnosis in 25% of patients in one study.¹

Laboratory features of NASH are nondiagnostic (Table 3). Mild to moderate elevations of serum aminotransferase levels are present in 70%–100% of patients with NASH.^{1,8,12,47} There is no significant correlation between the degree of serum aminotransferase elevation and the histologic features.^{9,12} Serum levels of aspartate transaminase (AST) are characteristically lower than those of alanine transaminase (ALT), which contrasts with the pattern usually seen in alcoholic hepatitis.^{7-9,12,48,51} Alkaline phosphatase levels may be mildly elevated in approximately one third of patients with NASH,^{7,8,10} but bilirubin and albumin levels are usually normal. The prothrombin time (PT) was increased in 53% of NASH patients in 1 series,¹ but other studies have shown that prolongation of the PT is unusual.^{26,48} A small percentage of patients with NASH may have low-titer ($\leq 1/320$) antinuclear antibody positivity.^{8,52} Antimitochondrial antibody, antibody to hepatitis B surface antigen, and hepatitis C virus (HCV) serology are negative.^{8,26} Ceruloplasmin and α_1 -antitrypsin levels are within normal limits.

Serum and hepatic iron stores may be elevated in patients with NASH. Bacon et al.⁸ documented abnormal results of serum iron studies (transferrin saturation and ferritin) in 18 (58%) of 31 patients with NASH, but none of their patients had histologic evidence of hemochromatosis. Subsequent studies of patients with NASH have shown increased serum ferritin levels in 53%–62% and elevated transferrin saturation in 11%–22%.^{9,14} Men with NASH may have higher iron stores than women.^{14,53} Despite the high prevalence of elevated iron stores in the setting of NASH, histologic or genetic evidence of genetic hemochromatosis is relatively uncommon.^{14,15} The available data do not support routine screening for genetic hemochromatosis in patients with NASH.

Table 3. Clinical and Laboratory Features of NASH

	Symptoms	Signs	Laboratory features
Common	Asymptomatic (48%–100%)	Hepatomegaly	2–4-fold elevation of ALT and AST AST/ALT < 1 in most cases Alkaline phosphatase slightly elevated in 1/3 Normal bilirubin, albumin, prothrombin time Elevated serum ferritin (53%–62%)
Uncommon	Vague right upper quadrant pain Fatigue Malaise	Splenomegaly Spider angiomas Palmar erythema Ascites	Low titer (<1/320) ANA Elevated transferrin saturation Cys282Tyr mutation of HFE gene

Table 4. Histologic Features of NASH

Features present in all or most cases
Macrovesicular steatosis
Parenchymal inflammation
Hepatocyte necrosis
Ballooning hepatocyte degeneration
Features observed with variable frequency
Perivenular, perisinusoidal, or periportal fibrosis
Mallory bodies
Glycogenated nuclei
Councilman bodies
Lipogranulomas
Stainable hepatic iron

Histology

NASH is indistinguishable histologically from alcoholic hepatitis. The major histologic features of NASH are summarized in Table 4. Unfortunately, minimal histologic criteria for NASH have not been established. Excessive histologic heterogeneity in published studies of NASH has led to significant clinical and pathologic discrepancies. In many studies, the histologic diagnosis of NASH has hinged on the presence of macrovesicular steatosis and lobular inflammation alone.^{1,8,9,12,14} Others have applied stricter histologic criteria, including macrovesicular steatosis, lobular inflammation, hepatocyte degeneration or hepatocyte ballooning, and/or hepatic fibrosis.^{5,51,54,55} This strict histologic definition of NASH has been advocated as an important step in standardizing the diagnosis of NASH and reducing the confusion about the epidemiology and natural history of this disease.^{54,56,57}

The fatty changes characteristic of NASH can affect the hepatic lobules either diffusely or primarily in the central zones.^{1,7,8,10,49} The degree of steatosis correlates with the BMI^{5,9} and is generally more severe in NASH than alcoholic hepatitis.^{48,49,51} Lobular inflammation of varying degrees is present in all cases and may consist of lymphocytes, other mononuclear cells, and neutrophils.^{1,7-10,12} Glycogenated nuclei are present in 35%–100% of cases of NASH.^{1,7,8,12,49} Hepatocyte ballooning and/or hepatocyte necrosis of varying degrees are usually present^{1,5,7,10,12,49,51,56} and have been required by some investigators to establish the diagnosis of NASH.^{5,54,56} Mallory bodies, which may be small, sparse, and inconspicuous, have been described in 10%–100% of patients with NASH.^{1,7,10,12,48,49,51} Mallory bodies may be more prominent in severe NASH.^{8,9} Councilman bodies¹ and lipogranulomas^{7,8} have been identified infrequently. Stainable iron may be present in 15%–65% of patients with NASH.^{1,8,11,14,15,56}

Pericellular, perisinusoidal, and periportal fibrosis have been described in 37%–84% of patients with

NASH.^{1,8-10,12,49,51} Fibrosis is most prevalent in zone 3 of Rappaport.^{9,48,56} Fibrosis may be more prevalent in children with NASH than in adults; in a small study of 14 children with NASH, portal fibrosis was present in all biopsy specimens.⁷ The extent of fibrosis may vary considerably, ranging from delicate strands surrounding small veins or groups of cells producing the so-called chicken wire fibrosis⁴⁸ to densely fibrotic septa with distortion of the hepatic architecture. Cirrhosis is found on initial biopsy in 7%–16% of patients with NASH.^{1,8,9,11,12,48,49,54} Histologic evidence of significant fibrosis or cirrhosis correlates poorly with clinical features and laboratory data,^{10,12,48,56} but investigators have shown that older age, obesity, and diabetes mellitus are independent predictors of the degree of fibrosis.^{5,9} Some investigators have suggested that increased hepatic iron is associated with an increased risk of fibrosis,¹⁴ and others have found no correlation between hepatic iron staining and fibrosis.^{8,9,11,15,21,50,53,56} Heterogeneity in patient selection, sample size, and study design may explain these seemingly contradictory results regarding the association between hepatic iron and fibrosis in the setting of NASH.

Pathogenesis

The pathogenesis of NASH is poorly understood. Hepatic steatosis, one of the hallmark histologic features of NASH, develops in the setting of multiple clinical conditions including obesity, diabetes mellitus, alcohol abuse, protein malnutrition, total parenteral nutrition, acute starvation, corticosteroid therapy, and carbohydrate overload. To understand how steatosis develops, one has to first understand how the liver metabolizes lipids under normal conditions. In the fed state, dietary triglycerides are processed by the enterocyte into chylomicrons, which are secreted into the lymph. The chylomicrons are hydrolyzed into fatty acids by lipoprotein lipase located in the capillary endothelium. These free fatty acids are transported to the liver, stored in adipose tissue as re-esterified triglycerides, or used as energy sources by muscle. Free fatty acids are also supplied to the liver in the form of chylomicron remnants, which are then hydrolyzed by hepatic triglyceride lipase. During fasting, the fatty acids supplied to the liver are derived from hydrolysis of triglycerides stored in adipose tissue. This reaction is mediated by a hormone-sensitive lipase, which is stimulated by catecholamines, glucagon, and growth hormone and inhibited by insulin. In the liver, the free fatty acids from all of these sources are oxidized by mitochondria, used for triglyceride synthesis, or used to form phospholipids and cholesterol esters.⁵⁸

Hepatic triglyceride accumulation occurs when there is a shift in fatty acid metabolism to favor net lipogenesis rather than lipolysis. This can occur when the amount of fatty acid supplied to the liver from the intestine or adipose tissue exceeds the amount needed for mitochondrial oxidation, synthesis of phospholipids, and synthesis of cholesterol esters. This is the presumed mechanism for steatosis in the setting of obesity,⁵⁹ diabetes mellitus,²⁴ excessive dietary intake of fats and carbohydrates, acute starvation, total parenteral nutrition,³² and protein-calorie malnutrition.⁶⁰ Hyperinsulinemia and insulin resistance may be a key component in the development of steatosis in obesity, diabetes mellitus, and protein-calorie malnutrition. Decreased fatty acid oxidation with subsequent fatty infiltration of the liver may also contribute to the genesis of steatosis, particularly in the setting of hyperinsulinemia.⁶¹ Triglycerides can also accumulate in the liver because of decreased synthesis of lipoproteins and decreased export of lipids from the liver. This accumulation may contribute to the development of steatosis in association with protein-calorie malnutrition,^{62,63} total parenteral nutrition,⁶⁴ and jejunioileal bypass.⁶⁵ Bacterial overgrowth and production of endotoxin may play a role in the development of steatosis in malnutrition and after jejunioileal bypass.⁶⁶ All of these mechanisms can lead to hepatic steatosis, which is presumed to be the "first hit" in the pathogenesis of NASH.⁶⁷

The exact stimulus that causes steatosis to progress to steatohepatitis and fibrosis in some patients is unclear. Alcoholic hepatitis and NASH are indistinguishable histologically, and it appears, not surprisingly, that these 2 distinct clinical entities share some common pathogenic mechanisms. The leading culprit for the induction of alcoholic hepatitis is lipid peroxidation and oxidative stress, which is also emerging as the best candidate for the "second hit" in the pathogenesis of NASH.⁶⁷ Ethanol induces hepatic cytochrome P450 2E1 (CYP2E1) in both animals and humans.^{68,69} Increased CYP2E1 expression is thought to contribute to the pathogenesis of alcoholic hepatitis through the generation of reactive oxygen metabolites that are capable of peroxidizing cellular membranes, resulting in cellular injury.⁷⁰ Recently, Weltman et al.⁷¹ showed that hepatic microsomal CYP2E1 expression is also increased in a rat nutritional model of NASH that closely mimics the histologic picture of NASH in humans. Immunohistochemistry showed that the pattern of CYP2E1 immunostaining in the rat livers closely followed the distribution of hepatic steatosis. In a subsequent study, the authors documented increased hepatic CYP2E1 in humans with NASH.¹⁶ In this study, the pattern of distribution of CYP2E1 was similar to that

found in alcoholic hepatitis and, as in the rat model, the immunostaining for CYP2E1 corresponded to the lobular distribution of steatosis. The investigators surmised that the increased expression of CYP2E1 in patients with NASH may result in the production of free oxygen radicals capable of inducing lipid peroxidation of hepatocyte membranes. In a recent study of a mouse model of NASH, hepatic CYP2E1 was up-regulated and was associated with a dramatic increase in total lipid peroxide levels in the liver that were substantially inhibited by anti-CYP2E1 antibody.⁷² This study confirmed that up-regulation of CYP2E1, which can be induced by fatty acids,⁷³ is a catalyst for hepatic lipid peroxidation in animal models of NASH. Confirmation of this finding in humans with NASH is awaited.

Induction of CYP2E1 probably is not the only cause of lipid peroxidation and oxidative stress in NASH. Berson et al.⁷⁴ showed recently that steatohepatitis-inducing drugs cause mitochondrial dysfunction and lipid peroxidation in rat hepatocytes without a change in the levels of CYP2E1. In this study, 4,4'-diethylaminoethoxyhexestrol, amiodarone, and perhexiline accumulated in mitochondria and inhibited both β -oxidation and respiration, resulting in a decrease in adenosine triphosphate (ATP) and an increase in mitochondrial formation of reactive oxygen species. These active oxygen metabolites oxidized fat deposits, causing lipid peroxidation. The authors suggested that lipid peroxidation caused nonselective destruction of the cytochrome P450 isoenzymes, whereas inhibition of mitochondrial β oxidation caused selective induction of CYP2E1, yielding no net change in CYP2E1 and a net decrease in most other cytochrome isoenzymes. These data suggest that induction of CYP2E1 is only one part of the complex pathogenesis of this disorder.

Lipid peroxidation is probably the most important pathogenic mechanism in NASH, but other factors probably contribute to the development of NASH, either by enhancing lipid peroxidation or by directly stimulating fibrogenesis and the inflammatory response characteristic of NASH. Recent studies suggest that hyperinsulinemia and insulin resistance have a role in the pathogenesis of NASH even in patients without glucose intolerance. Marchesini et al.²⁵ measured anthropometric and metabolic variables in 46 patients with fatty "bright" liver on ultrasound, elevated serum aminotransferase levels, and normal glucose tolerance. Of these patients with presumed NASH, 43% were overweight and 30% were obese; only 30% of the 92 control patients were overweight, and none were obese. They measured insulin resistance and insulin secretion using the homeostasis

model assessment method, which is calculated on the basis of fasting values of plasma glucose and insulin.⁷⁵ These investigators found that insulin resistance, hyperinsulinemia, lower glucose levels after a glucose load, and hypertriglyceridemia were associated with NASH irrespective of body weight, BMI, fat distribution, and glucose tolerance. Insulin resistance was the strongest predictor of NAFLD. Although this study was limited by methodologic flaws, especially the lack of histologic confirmation of the diagnosis of NASH, the findings are intriguing and supported by other studies that have shown that NAFLD, including NASH, coexists with other metabolic abnormalities of the IRS, including diabetes mellitus, hyperinsulinemia or impaired glucose tolerance, hypertriglyceridemia, obesity, and hypertension.^{26,76,77} Insulin resistance and hyperinsulinemia, which are characteristic of IRS, may lead to steatosis because high levels of insulin block mitochondrial fatty acid oxidation, leading to accumulation of triglycerides and fatty acids in the liver. Increased concentrations of intracellular fatty acids may be directly toxic to hepatocytes or lead to oxidative stress,⁷⁸ which leads to inflammation and fibrogenesis. Large, well-designed studies are needed to determine whether hyperinsulinemia is an independent contributor or simply a cofactor in the pathogenesis of NASH.

There is controversial evidence that hepatic iron may play a role in the pathogenesis of NASH. Bacon et al.⁸ documented abnormal ferritin and/or transferrin saturation in 58% of their patients with NASH, some of whom had slightly elevated hepatic iron concentration (HIC). However, there was no histologic evidence of hemochromatosis in any of these patients. In this study, it was not clear whether hepatic inflammation and steatosis led to increased serum ferritin and serum iron levels, iron accumulation was caused by heterozygosity for genetic hemochromatosis, or the mild increase in hepatic iron contributed to the liver injury in NASH. Theoretically, iron might contribute to the pathogenesis of NASH in several ways. Work in experimental models of iron overload has shown that iron induces lipid peroxidation of organelle membranes, resulting in membrane disruption, impaired mitochondrial oxidative metabolism, cellular injury, and cell death.^{79,80} In addition, iron activates lipocytes, stimulates collagen type I gene activation, and perpetuates lipocyte fibrogenesis.^{81,82} Thus, iron could potentially play a supporting role in the lipid peroxidation and fibrogenesis central to the development and progression of NASH.

The demonstration by Bacon et al.⁸ of hyperferritinemia and increased iron stores in NASH led to a flurry of

studies investigating the potential relationship between iron, HFE status, and NASH. Two studies seemed to support an association between HFE mutations, iron overload, and NASH. In a recent Australian study, George et al.¹⁴ examined the role of the Cys282Tyr HFE mutation in 51 patients with NASH and found a 31% prevalence of this mutation, which was much higher than the prevalence in the general population. Male sex and Cys282Tyr were significantly associated with increased transferrin saturation, stainable hepatic iron, HIC, and risk of fibrosis in NASH. Increased stainable iron was significantly associated with fibrosis, independent of Cys282Tyr mutation. Bonkovsky et al.¹⁵ found that NASH patients with either the Cys282Tyr or H63D HFE mutations had higher serum ferritin and transferrin saturation and significantly higher prevalence of stainable hepatic iron than patients without such mutations. These investigators could show no difference in HIC and hepatic iron index between patients with and without mutations and, contrary to the Australian study, did not show a significant correlation between HIC and fibrosis. In both the Australian and United States studies, most patients with mutations of HFE had normal HIC and many patients with increased HIC had no fibrosis, indicating an imperfect relationship at best between HFE status, hepatic iron concentration, and fibrosis in NASH.

Several recent studies have also failed to show an association between hepatic iron and fibrosis in NASH. Investigators from the Cleveland Clinic showed higher levels of hepatic iron accumulation in men than in women with NAFLD but showed no relationship between hepatic iron accumulation and aggressive histologic or clinical outcome in these patients.^{11,53} Mendler et al.²¹ examined the relationship between hepatic iron overload, insulin resistance, and liver injury in 161 non-Cys282Tyr-homozygous patients with unexplained iron overload. Most patients with iron overload had evidence of IRS, defined loosely in this study as BMI > 25, diabetes, hyperlipidemia, or any combination of these conditions. Steatosis was documented in 25% and NASH in 27%. There was no association between NASH and sex, IRS status, transferrin saturation, or HIC. Angulo et al.⁹ assessed the independent predictors of liver fibrosis in patients with NASH and found that increased transferrin saturation correlated positively with the severity of fibrosis in univariate analysis, but the association was abolished when controlled for age, obesity, diabetes, and AST/ALT ratio. The positive study by George et al.¹⁴ did not control for these factors, which may partially explain the discrepant results. In addition, none of the patients in the study by Angulo et al.⁹ had

increased HIC, which was present in 21% of the Australian patients. Several factors limit the comparability of all of the studies of HFE mutations, hepatic iron, and hepatic fibrosis in NASH, including geographically distinct patient populations, different histologic criteria for diagnosing NASH and NAFLD, different methodologies for assessing hepatic iron stores,⁸³ and incomplete data on HFE status.⁸⁴ This heterogeneity contributes to the prevailing confusion about these associations. Despite initial enthusiasm about the link between iron and NASH, the bulk of the available data suggest that HIC and HFE mutations play a minor role, at best, in the pathogenesis of NASH in the United States. Hyperferritinemia and mildly increased iron stores seen in some patients with NASH is most likely a result of the underlying necroinflammatory condition, which causes release of tissue iron and ferritin into the blood.⁹ However, because of the methodologic heterogeneity of the published studies, large studies examining the relationship between HFE mutations, HIC, and fibrosis in patients with NASH, controlling for potentially confounding factors such as obesity and diabetes mellitus, are justified.

Endotoxin and endotoxin-mediated cytokine release are suspected in the pathogenesis of alcoholic steatohepatitis, in which increased serum levels of bacterial endotoxin and lipopolysaccharide stimulate hepatic production of tumor necrosis factor (TNF)- α , interleukin (IL)-6, and IL-8 and activate an inflammatory response that incites hepatic necrosis.⁸⁵ Bacterial endotoxin may also contribute to the development of NASH in some circumstances. Portal endotoxemia was thought to contribute to NASH and hepatic failure associated with jejunoileal bypass,⁸⁶ the risk of which was reduced with metronidazole therapy.⁶⁶ Investigators at Johns Hopkins have demonstrated recently that genetically obese mice with severe steatosis have a much greater sensitivity to endotoxin than lean controls and develop NASH rapidly after exposure to low doses of bacterial lipopolysaccharide.⁸⁷ In addition, the genetically obese rats have decreased Kupffer cell function. The investigators postulate that obesity promotes liver injury via a complex mechanism that involves Kupffer cell dysfunction, impaired phagocytosis, and chronic low-grade systemic endotoxemia, which then creates the environment in which TNF- α and other cytokines damage sensitized hepatocytes through lipid peroxidation. The role of bacterial endotoxins and Kupffer cell dysfunction in the human form of NASH must be evaluated.

Mitochondrial changes and altered hepatic energy homeostasis may also have a role in the pathogenesis of NASH. Recent work has shown that the hepatic mito-

chondria of genetically obese (ob/ob) mice produce increased amounts of reactive oxygen species, with concomitant increases in uncoupling protein UCP-2, a mitochondrial protein that regulates ATP production.⁸⁸ Increased UCP-2 may be an adaptive response to obesity-related oxidative stress and confer a survival advantage to fatty hepatocytes. Up-regulation of UCP-2 might also decrease the efficiency of ATP synthesis, rendering fatty hepatocytes more vulnerable to liver injury from stresses that deplete hepatocyte ATP reserves.⁸⁹ Chavin et al.⁹⁰ have shown that ob/ob mice are less efficient than lean mice in replenishing ATP stores after minor surgical stress or transient hepatic hypoxia. These studies corroborate the work by Berson et al.,⁷⁴ which suggested a role for ATP depletion in drug-induced steatohepatitis. In a recent pilot study, Cortez-Pinto et al.⁹¹ showed that patients with NASH have severely impaired hepatic ATP homeostasis, with diminished capacity to recovery from hepatic ATP depletion, but the mechanism responsible for the defect in ATP response was not assessed. BMI correlated inversely with ATP recovery in NASH patients and controls, suggesting an interaction between obesity and energy homeostasis even in the absence of overt liver disease. This provocative line of investigation warrants further study to determine if mitochondrial dysfunction and ATP depletion, potentially mediated by up-regulation of UCP-2, is a cause or a consequence of NASH.

Fibrosis is a frequent histologic finding in NASH, but the inciting factors are not clear. Fibrosis occurs when lipocytes or Ito cells localized in the hepatic subendothelial space of Disse are activated. In NASH, lipid peroxides that are formed when the membranes of parenchymal cells are injured may mediate activation of the lipocytes. In addition, leukocytes and Kupffer cells may stimulate the lipocytes to proliferate, possibly through the release of fibrogenic cytokines such as transforming growth factor (TGF)- β .⁸² Once the lipocyte has been activated, platelet-derived growth factor (PDGF) and TGF- β may stimulate and sustain proliferation and fibrogenesis.

It is unlikely that one of these mechanisms explains the pathogenesis of NASH in all affected patients. More likely, NASH develops as a consequence of a 2-hit process, with the first hit being steatosis caused by a variety of mechanisms. After steatosis develops, a number of factors may incite the inflammatory response and fibrosis. The bulk of evidence supports oxidative stress as the essential second step in the process.⁹² However, it is becoming increasingly clear that lipid peroxidation, oxidative stress, inflammation, and fibrosis in NASH may

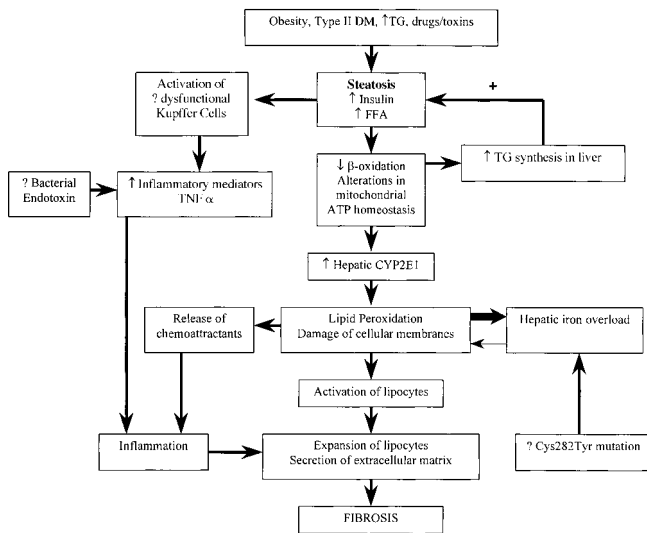


Figure 1. The pathogenesis of NASH is poorly understood. Obesity, type 2 diabetes mellitus, hyperinsulinemia, increased triglyceride levels, and certain drugs, toxins, and medical conditions can lead to increased serum fatty acids, which are then presented to the liver. Steatosis occurs when the supply of fatty acids in the liver exceeds that needed for triglyceride synthesis, mitochondrial oxidation, and phospholipid and cholesterol ester synthesis. After steatosis occurs, inflammation and fibrosis characteristic of NASH are probably stimulated by multiple factors. Increased expression of CYP2E1 may cause production of free oxygen radicals capable of inducing lipid peroxidation of hepatocyte membrane. Alterations in mitochondrial energy homeostasis may also contribute to hepatocellular injury. Hepatic iron overload, possibly associated with HFE gene mutations in some patients, may contribute to lipid peroxidation. Lipid peroxides damage cellular membranes with subsequent release of inflammatory mediators, including TNF- α . Inflammation ensues, which stimulates the fibrogenic cascade with expansion of the extracellular matrix, leading to fibrosis. The inflammatory response may also be stimulated by Kupffer cells and/or bacterial endotoxin in some cases. The actual interplay between all of these factors may differ, depending on the inciting condition for NASH.

be mediated by several factors, including CYP2E1 induction, bacterial endotoxin, iron, cytokines, Kupffer cell dysfunction, and altered ATP homeostasis. The exact interplay between these factors remains to be elucidated and will be the source of exciting scientific investigation in the future. Figure 1 shows a pathogenic scheme incorporating the suspected contributors to the development of NASH.

Natural History of NASH

The natural history of NASH is unknown, largely because there have been few long-term, prospective, longitudinal studies with histologic follow-up in patients with NASH. The available data suggest that NASH is a benign disease in most patients. However, in some patients, NASH can lead to cirrhosis, liver failure, or hepatocellular carcinoma. In 2 clinical series, the incidence of hepatic decompensation caused by progression

of NASH was 2%–3%.^{10,12} Only 3 studies have included histopathologic follow-up on a total of 28 patients.^{8,10,12} Repeat biopsies were performed 1–9 years after the histologic diagnosis of NASH was established. Combining the results of these 3 studies, histologic stability was found in 15 (54%) of 28, improvement in 1 (4%) of 28, and progression of fibrosis or cirrhosis in 12 (43%) of 28, including hepatocellular carcinoma in 1 patient. However, histologic progression did not signal clinical deterioration in most cases, and no clinical or laboratory data predicted the course of liver disease. These limited data suggest that NASH is an indolent condition with little clinical sequelae in most patients but can, in a small proportion of patients, progress to irreversible, clinically significant liver disease over a short period.

A recent study of 132 patients with NAFLD confirms that NASH is not always a benign disease.¹¹ In this study, the prevalence of cirrhosis was significantly higher among patients with NASH than among patients with steatosis without necrosis. In addition, the estimated yearly liver-related mortality for patients with NAFLD was much higher than that for the general United States population. Subgroup analyses showed that patients with NASH, defined in this study as steatonecrosis with either Mallory hyaline or fibrosis, had higher liver-related mortality than patients with fatty liver with or without nonspecific inflammation, although this difference did not reach statistical significance. The liver-related death rate in NASH was 11.0% compared with the United States, crude age-adjusted death rate of 9.5/100,000 per year for chronic liver disease/cirrhosis. These data suggest that the risk of liver-related mortality in NAFLD correlates, at least in part, with the degree of necrosis and/or fibrosis found at the index liver biopsy.

NASH and alcoholic steatohepatitis are identical histologically and may share some pathogenic mechanisms, but the prognosis and life expectancy of these disorders are very different. The 5-year survival rate of patients with alcoholic hepatitis is 50%–75% and is influenced by several factors, including the presence or absence of cirrhosis, nutritional status, and ongoing alcohol use.^{93,94} The long-term prognosis of NASH is not known. Propst et al.⁹⁵ found that 32 patients with NASH had lower life expectancy than age- and sex-matched controls from the normal population, but these differences were not statistically significant. The 5-year and 10-year survival probabilities in NASH patients were 67% and 59%, respectively, which were significantly higher than the 5-year and 10-year survival probabilities in 65 patients with alcoholic hepatitis (38% and 15%, respectively). Factors that modulate the life expectancy of patients with NASH

are not known, but older age, obesity, diabetes mellitus, and AST/ALT > 1 were shown in a recent study to be significant predictors of severe liver fibrosis (bridging/cirrhosis).⁹ It is reasonable to assume that patients with histologically advanced disease at diagnosis are more likely to suffer liver-related morbidity and mortality than those with more trivial forms of liver disease; however, this has not been proven.

Recent data suggest that NASH may be a major cause of cryptogenic cirrhosis. Caldwell et al.¹³ studied 70 consecutive patients with cryptogenic cirrhosis to assess major risks for liver disease. Diabetes mellitus and/or obesity were present in 74% of the patients with cryptogenic cirrhosis and were significantly more common in these patients than in patients with cirrhosis secondary to primary biliary cirrhosis or HCV. The prevalence of obesity and diabetes in patients with cryptogenic cirrhosis was similar to the prevalence of obesity and diabetes in 50 consecutive NASH patients who were, on average, a decade younger. These data suggest that these patients may arise from the same cohort. None of the patients with cryptogenic cirrhosis had evidence of NASH on liver biopsy, although 48% of patients had histologic evidence of mild to moderate macrosteatosis without necroinflammatory changes. Loss of substantial fatty infiltration has been documented in patients with NASH-associated cirrhosis,¹² which may explain the relative paucity of steatosis in these patients with cryptogenic cirrhosis. The AST/ALT ratio was significantly larger in patients with cryptogenic cirrhosis than in patients with NASH. AST/ALT ratio > 1 has been recognized as an independent predictor of liver fibrosis in NASH⁹ and may reflect impaired AST clearance by sinusoidal cells. Caldwell et al.¹³ have provided significant circumstantial evidence that NASH is the underlying cause of cryptogenic cirrhosis in some patients. Prospective studies of a large number of patients with NASH are eagerly awaited to establish the actual risk of progression of NASH to cirrhosis.

The natural history and prognosis of NASH are poorly understood, but it is clear that the prognosis of simple hepatic steatosis is favorable. In a recent study of 40 patients with nonalcoholic steatosis, 12 of 26 living patients had repeat liver biopsies after a median of 11 years.⁹⁶ None had progressed to steatohepatitis or cirrhosis. Of the remaining 14 patients, all had normal liver enzyme levels and normal liver ultrasound results. Of the 14 patients who died, none died of liver-related causes, and none had clinical evidence of liver disease before death. In another study, only 1 liver-related death occurred among 49 patients with simple steatosis.¹¹ These

studies confirm that nonalcoholic fatty liver, in the absence of NASH, is an extremely benign condition with little potential for histologic or clinical progression.

Diagnostic Strategies

The keys to establishing a diagnosis of NASH are presented in Table 5. Most patients with NASH are evaluated because of chronically elevated liver function test results, hepatomegaly, or both. The combination of history, physical examination, noninvasive blood tests, and radiologic examinations are useful for excluding other causes of liver disease. Laboratory testing should include a complete hepatic profile, complete blood count, PT, HCV antibody, hepatitis B surface antigen, iron indices, ceruloplasmin, antinuclear antibody, α_1 -antitrypsin, and antimitochondrial antibody. Hepatic ultrasonography, the preferred imaging modality, reveals a "bright" liver of increased echogenicity. Ultrasonography is 89%–95% sensitive and 84%–93% specific for steatosis but only 57%–77% sensitive and 85%–89% specific for fibrosis.^{97,98} Fatty liver can also be diagnosed by abdominal computed tomography scan, in which the liver is less dense than the spleen, and by magnetic resonance imaging, in which focal fat appears bright on T1-weighted imaging.

The most difficult aspect of establishing a diagnosis of NASH is distinguishing NASH from alcoholic hepatitis. Clinical, laboratory, and radiologic findings are generally unhelpful in differentiating NASH from alcoholic hep-

Table 5. Keys to the Diagnosis of NASH

Clinical
History of chronic mild elevation of serum aminotransferases
No history of significant alcohol use or abuse, confirmed by discussions with family members and primary care physician
Asymptomatic or nonspecific constitutional symptoms
No stigmata of chronic liver disease (except in patients with NASH-associated cirrhosis)
Laboratory
Serum aminotransferase levels 2–4 times the upper limits of normal
Remainder of liver function test results normal or near normal
Negative HbsAg, anti-HCV, AMA
ANA $\leq 1/320$
Normal ceruloplasmin, α_1 -antitrypsin, and transferrin saturation
Radiology (not required for diagnosis)
Bright (hyperechoic) liver on right upper quadrant ultrasound
Decreased density of liver compared with spleen on abdominal CT scan, usually diffuse but may be focal
Focal fat appears bright on T1-weighted imaging
Histology
Alcoholic hepatitis-like picture: diffuse or centrilobular macrovesicular steatosis, ballooning hepatocytes, hepatocyte necrosis, mixed lobular inflammatory infiltrate, with or without fibrosis, Mallory bodies, lipogranulomas, and glycogenated nuclei

atitis in ambulatory patients.^{49,51} Alcoholic hepatitis and NASH are identical histologically; therefore the diagnosis of NASH can be entertained only in the absence of significant alcohol use (defined in most published studies as less than 20–40 g of alcohol per day). A detailed history of alcohol intake should be obtained from the patient, family members, and the primary care provider. Unfortunately, laboratory markers, such as the ratio of AST to ALT, γ -glutamyl transferase, and mean corpuscular volume, lack sufficient sensitivity and specificity to diagnose chronic excessive alcohol consumption.⁹⁹ The serum mitochondrial AST/total AST ratio has been investigated as a marker of chronic alcoholism but has poor specificity, especially in the setting of NASH.^{100,101} The ratio of desialylated transferrin to total transferrin has 81% sensitivity and 98% specificity to identify patients with excessive alcohol intake,¹⁰¹ but this laboratory test is most accurate for male patients with daily alcohol intake of ≥ 40 –60 g/day and is not routinely available.

The role of the liver biopsy in establishing the diagnosis of NASH has been debated. Many practitioners consider NASH a diagnosis of exclusion. The diagnosis is often made when clinical and laboratory examinations fail to reveal another cause of chronic liver disease and a radiologic study provides evidence of fatty liver. This practice is imperfect and unfortunate. One study showed that the positive predictive value of the pre-biopsy diagnosis was only 56% for fatty liver.¹⁰² NASH is a histologic diagnosis, and liver biopsy is the only diagnostic test that can reliably identify and quantify hepatic steatosis, inflammation, necrosis, and fibrosis. There is poor correlation between clinical, laboratory, and histologic findings in NASH; therefore, it is impossible to stage patients with NASH without histologic data. In addition, measurement of hepatic iron may have important prognostic and therapeutic implications in the future, and this can only be quantified from liver tissue. For all of these reasons, many hepatologists recommend that a liver biopsy be performed in all patients with a presumptive diagnosis of NASH. This recommendation is sound despite the small risk of complications from a liver biopsy and limited treatment options for NASH that are unlikely to be altered by the results of a liver biopsy.

Treatment of NASH

The optimal therapy for NASH has not been established in adults (Table 6). Weight loss has resulted in normalization of biochemical and ultrasonographic abnormalities in children with NASH,¹⁰³ but this approach has not been examined in a controlled manner in adults. Knobler et al.⁷⁶ evaluated 48 patients with chron-

Table 6. Possible Treatment for NASH

Moderate, sustained weight loss
Control of diabetes mellitus and hyperlipidemia
Ursodeoxycholic acid
Gemfibrozil
Metformin
Betaine
Vitamin E, other antioxidants
Thiazolidinediones

None of these treatments have been evaluated in large clinical trials of adult patients with NASH.

ically elevated liver enzymes with clinical, ultrasound, and histologic findings consistent with fatty liver with or without inflammatory change, and no other identifiable cause of liver disease. Of these patients, 81% were obese, 73% were glucose-intolerant or diabetic, and 85% had dyslipidemia. Treatment included dietary intervention as well as lipid-lowering and oral hypoglycemic medications as needed. These interventions resulted in moderate weight loss, improved serum lipid profile and fasting blood glucose, as well as a substantial reduction in serum liver enzyme levels in 96% of patients. However, serial liver biopsies were not performed, so the relationship between improved liver chemistries and liver histology could not be established. Others have reported similar improvement in liver chemistries and/or histology after weight loss in a small number of patients with NASH.^{104,105} These studies suggest that the biochemical and histologic improvement seen in children with NASH after weight reduction can also be obtained in adults after sustained weight reduction, but large prospective studies with liver biopsy before and after weight loss are needed to confirm this finding. Rapid weight loss has been associated with exacerbation of steatohepatitis in morbidly obese patients^{106,107}; therefore, weight loss should be moderate and monitored carefully.

Medical therapy for NASH has unproven benefit. Laurin et al.¹⁰⁸ conducted a small pilot study of ursodeoxycholic acid (UDCA) and clofibrate in the treatment of NASH. Treatment with UDCA resulted in significant improvement in liver chemistries and hepatic steatosis but no significant change in histologic grade of inflammation or fibrosis. Clofibrate, which was given to NASH patients with hypertriglyceridemia, was of no clinical benefit in the treatment of NASH. Gemfibrozil, a medication that reduces very low-density lipoprotein triglyceride production, was evaluated in a small controlled study of 46 patients with NASH.¹⁰⁹ After 4 weeks of treatment, serum aminotransferase levels were significantly decreased in 74% of the gemfibrozil group compared with 30% in the control group. Responses did not correlate with pretreatment serum triglyceride levels.

Serial liver biopsy data were not reported, and the durability of biochemical response was not evaluated. Despite these significant limitations, the results of this small study suggest that gemfibrozil should be investigated further in long-term, randomized, placebo-controlled trials in patients with NASH. Betaine, a metabolite of choline, was evaluated recently in a small pilot study for the treatment of NASH.¹¹⁰ Ten patients with NASH were given a 12-month course of oral betaine anhydrous solution (20 g/day). Three of 7 patients who completed the study had normalized serum aminotransferase levels on therapy, and 3 patients had a 50% decrease in serum aminotransferase levels. Histologic improvement was noted in 50%. Betaine was well tolerated, although 40% of patients developed mild side effects that were not dose limiting. Based on these limited findings, this novel agent warrants further evaluation as a treatment for NASH.

Medications that minimize oxidative stress may prove useful in the treatment of NASH. Vitamin E, a potent antioxidant, has been studied in a small, open-label study of 11 pediatric patients with presumed NASH.¹¹¹ Diagnosis was based on the presence of chronically elevated transaminase levels, fatty liver on ultrasound, and no other demonstrable reason for transaminitis other than obesity. Two patients had biopsy-proven NASH. Patients were prescribed 400–1200 IU of oral vitamin E daily. Treatment was well tolerated and resulted in normalization of liver function test results during treatment; however, the liver remained diffusely echogenic during treatment. Biochemical improvement was not sustained when vitamin E was discontinued. The lack of histologic data before and after vitamin E therapy limits the clinical impact of this pilot study, but additional studies of vitamin E and possibly other antioxidants in pediatric and adult patients with biopsy-proven NASH are warranted.

The association of hyperinsulinemic insulin resistance with NASH provides a possible target for treatment. Metformin, a biguanide that reduces hyperinsulinemia and improves hepatic insulin resistance, is used as an oral hypoglycemic in patients with diabetes. A recent study by Lin et al.¹¹² showed that metformin, but not caloric restriction, greatly reduced hepatomegaly and hepatic steatosis in ob/ob mice with associated insulin resistance without significant reduction in fasting serum glucose concentrations. The investigators postulated that metformin may improve hepatic insulin resistance by decreasing hepatic expression of TNF- α , a cytokine that promotes insulin resistance and may incite the necroinflammatory lesions characteristic of NASH. Troglita-

zone, a thiazolidinedione that improves insulin resistance and hyperinsulinemia, was investigated in a pilot study of 6 patients with biopsy-proven NASH.¹¹³ Patients received 200 mg of troglitazone twice daily, which was well tolerated. Four (67%) of 6 patients had normalization of ALT levels on therapy, and normalization persisted in the 3-month follow-up period after discontinuation of troglitazone. No patient lost weight during the treatment period. These results were encouraging; however, the Food and Drug Administration removed troglitazone from the market in March 2000 because of rare but serious hepatotoxicity. Further human studies are anxiously awaited that will evaluate the effectiveness of metformin and other insulin-sensitizing medications, including new thiazolidinediones, in hyperinsulinemic patients with NASH.

Patients with NASH who develop end-stage liver disease should be evaluated for liver transplantation. The outcome of liver transplantation in these patients appears to be good, although NASH can recur after liver transplantation.^{114–116} The causes for recurrent NASH after liver transplantation are unknown but are probably multifactorial, including persistent hypertriglyceridemia, obesity, diabetes mellitus, and corticosteroid therapy.

Summary

NASH is a chronic disorder that is recognized increasingly in patients with abnormal liver function test results. Most patients are female and obese with evidence of type 2 diabetes mellitus and/or hyperlipidemia. However, NASH can also occur in lean male and female patients without these associated conditions. NASH is indistinguishable histologically from alcoholic hepatitis and is usually characterized by macrovesicular steatosis, necroinflammation, ballooning hepatocyte degeneration, and fibrosis; however, strict histologic criteria for NASH have not been established. The pathogenesis of NASH is poorly understood, but evidence supports oxidative stress as the most important factor. A diagnosis of NASH should be considered in patients with abnormal liver function test results, no history of alcohol abuse, negative results of laboratory evaluation for other causes of chronic liver disease, and evidence of hepatic steatosis on an imaging study. However, NASH is a histologic diagnosis; therefore, liver biopsies should be performed to establish the diagnosis and assess the degree of steatosis and fibrosis. NASH is a stable, relatively benign condition in most patients, but cirrhosis is found on index biopsy specimens in 7%–16%, and progression to cirrhosis and end-stage liver disease has been documented. There is no established medical treatment for NASH,

but moderate sustained weight loss is the mainstay of therapy. Treatments aimed at the various pathogenic mechanisms that lead to the development of NASH are sorely needed. Orthotopic liver transplantation should be performed in appropriate patients with end-stage liver disease secondary to NASH. Large prospective studies of patients with NASH will provide much-needed information about the natural history and prognosis of this poorly understood disorder.

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