Nonalcoholic Fatty Liver Disease

Series Editor:
Richard A. Wright, MD
Professor and Chief, Division of Gastroenterology/Hepatology, Department of Medicine, University of Louisville School of Medicine, Louisville, KY

Contributors:
Matthew Cave, MD
Fellow, Division of Gastroenterology/Hepatology, Department of Medicine, University of Louisville School of Medicine, Louisville, KY

Miriam Vos Louthan, MD, MSPH
Fellow, Division of Gastroenterology, Department of Pediatrics, University of Louisville School of Medicine, Louisville, KY

Craig J. McClain, MD
Professor and Vice Chair for Research, Department of Medicine; Jewish Hospital Distinguished Chair in Hepatology, Division of Gastroenterology/Hepatology; University of Louisville School of Medicine, Louisville, KY

Table of Contents

Case Vignette .................................................. 2
Introduction .................................................. 2
Epidemiology ............................................... 3
Pathogenesis ............................................... 4
Natural History and Prognosis ......................... 5
Clinical Evaluation ......................................... 6
Treatment .................................................. 8
Conclusion ................................................ 10
References ............................................... 10

Cover Illustration by Christine Armstrong

Copyright 2005, Turner-White Communications, Inc., Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications. Turner White Communications retains full control over the design and production of all published materials, including selection of appropriate topics and preparation of editorial content. The authors are solely responsible for substantive content. Statements expressed reflect the views of the authors and not necessarily the opinions or policies of Turner White Communications. Turner White Communications accepts no responsibility for statements made by authors and will not be liable for any errors of omission or inaccuracies. Information contained within this publication should not be used as a substitute for clinical judgment.

www.turner-white.com
Nonalcoholic Fatty Liver Disease

Matthew Cave, MD, Miriam Vos Louthan, MD, MSPH, and Craig J. McClain, MD

CASE VIGNETTE
An obese 55-year-old white man with diabetes and hypertriglyceridemia develops right upper quadrant discomfort. He is subsequently diagnosed with symptomatic gallstones and undergoes laparoscopic cholecystectomy at a regional hospital. On intraoperative examination, his liver appears fatty and nodular; biopsy shows steatohepatitis with cirrhosis. The patient is referred to a hepatology clinic.

At the clinic, the patient says he does not drink alcohol excessively and has no family history of liver disease. He is fatigued and reports persistent right upper quadrant fullness. Physical examination reveals nontender hepatomegaly and prominent central obesity with a body mass index (BMI) of 40 kg/m². Results of laboratory tests include alanine aminotransferase (ALT) level of 85 U/L, aspartate aminotransferase (AST) level of 75 U/L, and an albumin level of 2.9 g/dL; results of all other laboratory tests are normal. The patient is diagnosed with nonalcoholic steatohepatitis and is instructed to lose weight and control his diabetes and hypertriglyceridemia.

Over the next 3 years, the patient is noncompliant with the recommended lifestyle modifications, despite input from his physician, a nutritionist, and family members. The patient’s liver function deteriorates, and he develops ascites complicated by noncompliance with a low sodium diet. He ultimately requires high-dose spironolactone and furosemide. On a subsequent screening ultrasound, a 3-cm mass is noted; biopsy shows hepatocellular carcinoma. The patient is referred to a liver transplant program; however, the patient’s severe obesity is considered to be a major risk factor for complications of liver transplantation.

Faced with imminent mortality, the patient attempts to lose weight and adhere to the low sodium diet. He presents to his local emergency room in pulseless electrical activity arrest with severe hyperkalemia and dies despite aggressive resuscitation attempts. Possibly, this poorly compliant patient used potassium-containing salt substitute, despite medical counseling regarding this risk. He is survived by 2 adult sons, one of whom is obese and was recently diagnosed with prediabetes and elevated liver enzyme values.

INTRODUCTION

Obesity-associated fatty liver disease was first described by Westwater and Fainer1 nearly 50 years ago. Knowledge of the disease progressed little until 1979, when Adler and Scaffner2 described fatty liver, hepatitis, fibrosis, and cirrhosis mimicking alcoholic liver disease in a group of overweight patients, many of whom were diabetic and had lipid abnormalities. The following year, Ludwig et al3 introduced the term nonalcoholic steatohepatitis to describe similar pathologic findings in a group of obese female patients, many of whom were diabetic, with hepatomegaly and mild abnormalities on liver function tests. Since then, the term nonalcoholic fatty liver disease (NAFLD) has been used to describe a larger spectrum of steatotic liver disease generally associated with the metabolic syndrome (Table 1).

NAFLD is defined by clinicopathologic criteria. Clinically, patients with NAFLD do not consume significant quantities of alcohol (generally no more than 2 drinks per day). Pathologically, several patterns of disease exist in NAFLD that resemble alcoholic liver disease. The sine qua non of NAFLD is macrovesicular steatosis or fatty liver. If this condition exists in isolation, the patient is diagnosed with nonalcoholic steatohepatitis and is instructed to lose weight and control his diabetes and hypertriglyceridemia.

Primary NAFLD is the hepatic manifestation of the metabolic syndrome and its prevalence is increasing at an alarming rate. Secondary causes of NAFLD are much less common and include drugs and toxins, surgical procedures, and other causes as noted in Table 2. This review focuses on primary NAFLD.
The precise prevalence of NAFLD is difficult to assess because it is unethical to perform liver biopsies in population-based screening studies of asymptomatic individuals; however, the prevalence of NAFLD has been estimated by various approaches. These methods include population-based screening studies that noninvasively define NAFLD by either laboratory or ultrasonic findings; autopsy studies of accidental or hospital deaths; and biopsy or radiologic studies in select patients as noted in the following discussion.

**POPULATION-BASED LIVER ENZYME STUDIES**

Several analyses of the Third National Health and Nutrition Examination Survey (NHANES III) database of the US population from 1988 to 1994 have provided information regarding the prevalence of NAFLD in the general adult and adolescent populations. In an analysis of 15,676 adult members of the NHANES III data set, 7.9% of the general US adult population had abnormal transaminase values. Only 2.5% of this population had liver disease attributable to hepatitis B, hepatitis C, iron overload, or alcohol. Unexplained transaminitis, most likely caused by NAFLD, occurred in 5.4% of the population or 9.1 million adult Americans. This prevalence estimate was consistent with that found in the similar, previously published Dionysos study of Northern Italians (8.8%). However, using the newly reduced normal values for ALT, the prevalence of NAFLD in the US adult population would have been 21.2%. In a similar study of 2450 US adolescents (ages 12 to 18 years) in the NHANES III database, transaminitis not caused by hepatitis B, hepatitis C, or iron overload was examined. When alcohol use was not excluded, 1.5% of normal-weight adolescents (BMI < 85th percentile) had an elevated ALT level compared with 5% of overweight adolescents (BMI in the 85th to 95th percentile) and 9.5% of obese adolescents (BMI > 95th percentile). Even without alcohol ingestion, however, obese adolescents were 4 times more likely to have abnormal serum ALT levels than adolescents of normal weight, suggesting that NAFLD is an important problem in this population.

**POPULATION-BASED ULTRASOUND STUDIES**

Transaminase evaluation may not detect a substantial proportion of patients with NAFLD because many of these patients do not have elevated ALT or AST levels. Ultrasound studies have been used as a screening tool but are limited because ultrasonography cannot distinguish simple steatosis from steatohepatitis and may not detect mild steatosis. In an ultrasound study...
of 4009 Chinese administrators who did not consume alcohol regularly, 12.9% had fatty liver. Among 2574 residents of Japan, 14% had ultrasonographic fatty liver associated with alcohol use, obesity, and hypertriglyceridemia. In the Dionysos study, ultrasound examination of 257 Northern Italians without viral hepatitis revealed that obesity and alcohol consumption combined synergistically to produce fatty liver. Hepatic steatosis was detected in 16% of nonobese nondrinkers, 46% of nonobese drinkers, 76% of obese nondrinkers, and 95% of obese drinkers.

POSTMORTEM LIVER HISTOLOGY FROM ACCIDENTAL AND HOSPITAL DEATHS

Postmortem liver tissue studies are surrogates for the ideal population-based liver biopsy study if the deaths are known to be truly accidental, if the patients are not selected, and if the patients are presumably without significant symptomatic liver disease. A limitation is that excluding a history of alcohol consumption in these patients is difficult, if not impossible. In a study of 423 deceased crewmembers from fatal aircraft accidents in the United Kingdom, 16% had fatty liver. In a subsequent study of 166 young British men (mean age of 29 years) who died accidentally but not as victims of alcohol-related traffic accidents, 21% had hepatic steatosis. In a Danish study of 503 consecutive autopsies for traffic fatalities in nonalcoholic persons, 24% had fatty liver and 7% had nonspecific portal inflammation. In a Canadian autopsy study of 351 unselected hospital deaths of nonalcoholic patients, 18.5% of obese subjects had steatohepatitis and 13.8% had fibrosis compared with 2.2% and 6.6% in lean patients. In a study of 678 consecutive autopsies in Denmark, slight fatty changes were observed in 43%, moderate fatty changes in 9%, and severe fatty changes in 2%.

SUMMARY

Summarizing these data from the population-based laboratory, ultrasound, and autopsy series, the estimated overall prevalence of simple steatosis is 20% to 30%, and the prevalence of NASH is 2% to 3%. Therefore, NAFLD is now the most common liver disease.

PATHOGENESIS

Although the exact mechanisms of NAFLD and NASH are not yet completely understood, animal models as well as human studies have provided many clues. The pathogenesis is most likely multifactorial, combining a genetic predisposition with environmental influences similar to the presumed causes of obesity. Obesity and insulin resistance are nearly universal in patients with NAFLD and NASH. Insulin is an important modulator of glucose, lipids, and even cytokines, all of which likely play key roles in the development of NAFLD and NASH. In addition to the baseline steatosis that occurs in NAFLD, a second stressor can induce inflammation and scarring leading to the injury seen in NASH. Potential second stressors include cytokine dysregulation, oxidative stress, and mitochondrial dysfunction.

INSULIN RESISTANCE

Insulin promotes lipid storage and inhibits lipolysis. Insulin resistance has been implicated in the pathogenesis of NAFLD by multiple epidemiologic studies, and, as noted previously, NAFLD is proposed to be the hepatic manifestation of the metabolic syndrome. Although not every patient with NAFLD meets the definition of the metabolic syndrome (Table 1), most patients with NAFLD show evidence of insulin resistance. Marchesini et al reported hyperinsulinemia and insulin resistance in subjects with ultrasonographic evidence of fatty liver. This study found that insulin resistance was more closely related to hepatic fat than to BMI, suggesting an independent role of insulin resistance.

Understanding carbohydrate and lipid metabolism as regulated by insulin can help explain potential sources for the fat (primarily triglycerides) stored predominantly in macroparticles in steatosis. Storage occurs when the synthesis or intake of triglycerides into the liver exceeds the ability to export or metabolize the lipids. Insulin resistance may induce increased synthesis and storage of fats in the liver as well as increased deposition of recirculated fatty acids from peripheral fat.

The difference between the negative effects of central obesity, which is clinically associated with both insulin resistance and NAFLD, versus peripheral obesity is unclear. Recent studies have shown that visceral and peripheral adipose tissue differ qualitatively in terms of products and metabolic actions. Compared with peripheral fat during lipolytic activity, visceral fat releases more fatty acids, which are delivered directly into the portal vein for transport into the liver. Visceral fat also releases more tumor necrosis factor (TNF) and less adiponectin, an anti-inflammatory cytokine. These factors may help explain the association of central adiposis with both the metabolic syndrome of insulin resistance and NAFLD.

CYTOKINE DYSREGULATION

Abnormal cytokine metabolism is a major feature of NASH. TNF is an important pro-inflammatory cytokine
that is actively produced by adipocytes as well as by immune cells. TNF is not only important in the pathogenesis of NASH because of its pro-inflammatory properties, but also because it is a regulator of insulin and likely contributes to insulin resistance. NASH has been associated with increased TNF production in both animal models and obese patients with NASH.21,25

Another important cytokine disturbance in NAFLD is a decreased level of adiponectin. Adiponectin is an insulin-sensitizing, anti-inflammatory adipokine exclusively secreted by adipose cells. The more obese the individual, the lower the circulating adiponectin level compared with normal-weight and thin patients, obese patients have adiponectin deficiency. Adiponectin has been shown to be anti-inflammatory at the endothelial level in cardiac vessels and correlates with insulin and glucose. Low adiponectin levels are associated with increased insulin resistance and higher fasting glucose. In children [Louthan MV, Stutts J, Sullivan J, McClain CJ, unpublished data, 2005] and adults with NAFLD, adiponectin levels are even lower than in obese patients who are otherwise healthy, which suggests that adiponectin may play a key role in the liver disease.26 In animal models, subjects with steatohepatitis have demonstrated adiponectin deficiency, and adiponectin supplementation has been shown to improve steatosis and liver injury.27 This effect may be related in part to the complex interactions between adiponectin and TNF, in which adiponectin decreases TNF.

MITOCHONDRIAL DYSFUNCTION

Mitochondria are dysfunctional in NAFLD and are an important area of NASH research, not only as a key source of reactive oxygen species but also because of their role in lipid metabolism. Structural abnormalities of the hepatic mitochondria are commonly seen on liver biopsy, including swollen, enlarged mitochondria with crystalline bodies. These structural abnormalities are mirrored by disturbances in the ATP-producing mitochondrial electron transport chain. Animal studies have shown decreased ATP in rats with fatty liver.28 Perez-Carrera et al31 showed dysfunction in all the components of the mitochondrial respiratory chain in a study of 38 NASH patients.

GENETIC FACTORS

By modulating the response to overnutrition, single nucleotide polymorphisms in genes governing metabolism, inflammation, fibrosis, and repair contribute to development and progression of NAFLD. Although beyond the scope of this paper, progress in this emerging field has recently been reviewed by Day.32

NATURAL HISTORY AND PROGNOSIS

An understanding of the natural history of NAFLD is incomplete because of the lack of large, prospective, long-term clinical studies with histologic follow-up data for the various forms of NAFLD. Available data suggest that, although the disease is benign in most patients, some develop cirrhosis and hepatocellular carcinoma and die from a liver-related cause.

Simple steatosis carries the best prognosis, and it progresses infrequently.33–35 In contrast, NASH commonly progresses both clinically and histologically. In a meta-analysis of 6 retrospective repeat liver biopsy studies of noncirrhotic patients with NASH, Fassio et al38 observed that progressive fibrosis occurred in 39.3% of patients within 1.2 to 15.7 years. In a prospective, longitudinal study of liver biopsy published in the same article, Fassio and colleagues found that 31.8% of patients with NASH had progressive fibrosis on repeat biopsy occurring at a median of 4.3 years after the first biopsy. Furthermore, NASH may progress to histologic cirrhosis in up to 15% of patients.39 When patients with biopsy-confirmed NASH were followed for approximately 10 years, 25% developed clinical cirrhosis, 40% died, and 11% died from a liver-related cause.34

Although the risk is currently unknown, some cirrhotic patients with NASH develop hepatocellular carcinoma. As recently reviewed by Caldwell et al,40 obesity and diabetes are significant risk factors for both NAFLD and hepatocellular carcinoma. Cryptogenic cirrhosis, likely secondary to NASH, has accounted for 6.9% to 29% of cases of hepatocellular carcinoma.41,42

NAFLD may complicate other liver diseases, such as hepatitis C infection and alcoholic liver disease. In chronic hepatitis C infection, the prevalence of steatosis on liver biopsy is approximately 50%, which is approximately 2.5-fold higher than expected by chance

www.turner-white.com
Nonalcoholic Fatty Liver Disease

Table 3. Signs, Symptoms, and Laboratory Findings Associated with Nonalcoholic Fatty Liver Disease

<table>
<thead>
<tr>
<th>None</th>
<th>Vague abdominal discomfort</th>
<th>Fatigue and malaise</th>
<th>Right upper quadrant discomfort</th>
<th>Hepatomegaly</th>
<th>Elevated aminotransferases</th>
<th>Normal synthetic function</th>
</tr>
</thead>
</table>

Adapted with permission from Reid BM, Sanyal AJ. Evaluation and management of non-alcoholic steatohepatitis. Eur J Gastroenterol Hepatol 2004;16:1118.

Alcoholic liver disease, although pathologically indistinguishable from NAFLD, has an increased prevalence and severity in obese patients. In the previously discussed Dionysos study, obesity and ethanol acted synergistically to produce steatosis more frequently than either risk factor alone. Excess body weight appears to be a risk factor for the progression of fibrosis in alcoholic liver disease.

CLINICAL EVALUATION

NAFLD is a diagnosis of both inclusion and exclusion. Evaluation thus relies on a thorough history and physical examination that must be supported by noninvasive blood tests and radiologic studies. Liver biopsy, although controversial, may be required.

PATIENT DEMOGRAPHICS

Although NAFLD may occur at any age, disease onset is most common in middle age. Racial variations may exist for NAFLD: In the United States, compared with whites, Hispanics are at particularly high risk, whereas blacks are relatively spared. Although initially described in women, NAFLD is now believed to affect men at least as frequently—if not more frequently—than women.

MEDICAL HISTORY

Most NAFLD patients are evaluated because of incidental abnormal findings on liver function tests. Asymptomatic patients with risk factors for NAFLD should be screened for the disease. Patients may present with symptoms including fatigue, malaise, and sensation of right upper quadrant fullness or discomfort (Table 3). Very few patients have symptoms consistent with cirrhosis. Furthermore, secondary causes of NAFLD must be excluded (Table 2).

Particular attention should be paid to the associated metabolic risk factors, including the metabolic syndrome, obesity, type 2 diabetes mellitus, and dyslipidemia. It now appears that the majority of NAFLD patients may have the metabolic syndrome, and its presence may be predictive of worse disease. In an Italian study, 53% of patients with simple steatosis and 88% of patients with NASH fulfilled ATP III criteria for the metabolic syndrome.

Historically, obesity has been the risk factor most strongly associated with NAFLD. In liver biopsies obtained in obese patients, 48% to 60% had steatosis, 9% to 26% had steatohepatitis, 8% to 32% had fibrosis, and 2.7% to 4% had cirrhosis. NAFLD is even more prevalent in extremely obese patients. In morbidly obese patients undergoing bariatric surgery, 85% to 94% had steatosis, and 24% to 36% had steatohepatitis, 35% to 74% had fibrosis, and 0 to 4% had cirrhosis. At a Brazilian obesity clinic, one-third of nondiabetic female patients had fatty liver by ultrasound. Body fat distribution also seems to be significant, with central and visceral obesity an emerging risk factor, even in patients with a normal BMI.

After obesity, type 2 diabetes is the risk factor most commonly associated with NAFLD. Type 2 diabetes has been reported in 10% to 55% of NAFLD patients. Diabetic men are twice as likely to develop NAFLD than healthy men, and the prevalence of fatty liver by ultrasound in unselected diabetic patients is 25%. Likewise, dyslipidemia is common in NAFLD patients and has been reported in 21% to 80% of cases. Although hypercholesterolemia has been reported, the most common dyslipidemias include hypertriglyceridemia and low high-density lipoprotein levels. Half of unselected lipid clinic patients had fatty liver by ultrasound.

Several commonly used medications, including amiodarone, tamoxifen, glucocorticoids, and possibly calcium channel blockers, are causes of secondary NAFLD and should be excluded.

SOCIAL AND FAMILY HISTORY

Because significant alcohol consumption excludes
the diagnosis of NAFLD, an accurate history of alcohol consumption must be obtained. It may be necessary to corroborate the patient’s history with family members. Some alcohol consumption is, however, permissible. Although the acceptable consumption rate has ranged from 10 to 40 g daily of ethanol in various studies, 20 g daily has been considered a reasonable compromise. Therefore, patients who consume more than the equivalent of two 5-oz glasses of wine daily do not have NAFLD by definition. Additionally, the clinician should screen for risk factors for viral hepatitis such as intravenous drug abuse and high-risk sexual behavior. Occupational history may reveal exposure to petrochemicals, a cause of secondary NAFLD.

Patients may have a positive family history of liver disease. In a research setting, 18% of NASH patients had an affected first-degree relative. Familial clustering is not surprising because both the metabolic syndrome and NAFLD are likely modulated by genetic factors. Other familial liver diseases may also be detected, such as Wilson’s disease and α1-antitrypsin deficiency, as well as alcoholic liver disease and vertical transmission of viral hepatitis.

**PHYSICAL EXAMINATION**

Unless the NAFLD patient is cirrhotic, the commonly appreciated stigmata of chronic liver disease are usually absent. Hepatomegaly is the only common physical examination finding and is present in up to 75% of NAFLD patients. The remainder of the physical examination should focus on the detection of the metabolic syndrome. Therefore, vital signs including height, weight, and blood pressure must be accurately assessed. In addition, waist circumference should be measured and the skin should be examined for acanthosis nigricans, a marker of insulin resistance.

**LABORATORY STUDIES**

Routine laboratory testing should be performed to confirm the presence of liver disease, to detect diabetes and dyslipidemia, and to rule out the other common hepatic diseases. Recommended tests include a comprehensive metabolic panel, a fasting lipid panel, prothrombin time, complete blood count, viral hepatitis serologies, iron studies, antinuclear antibody, antimitochondrial antibody, anti–smooth muscle antibody, α1-antitrypsin level, ceruloplasmin in young patients, thyroid-stimulating hormone, and either a fasting glucose or hemoglobin A1c.

Although liver function tests are usually abnormal in patients with NAFLD, test results may be normal, even in advanced disease. The most frequently observed abnormalities are mild elevations in aminotransferases, which are generally less than 4 times the upper limit of normal. In contrast to alcoholic liver disease, the AST to ALT ratio in NAFLD is usually less than 1. In the presence of advanced fibrosis, however, the ratio may be between 1 and 2. Alkaline phosphatase may be elevated to values less than twice the upper limit of normal. Neither the presence nor the degree of transaminase elevation reliably predicts severity of disease. Complete blood count, bilirubin, and tests of liver synthetic function (eg, albumin, prothrombin time) are usually normal unless the patient is cirrhotic. In diabetic patients with NAFLD, hypoalbuminemia should trigger evaluation for proteinuria caused by diabetic nephropathy.

Low titers of autoimmune antibodies are present in up to one-third of NAFLD patients and most frequently represent a nonspecific inflammatory response rather than autoimmune hepatitis. Of these antibodies, anti-nuclear antibodies are most commonly elevated, although anti–smooth muscle antibody may be found in up to 6% of patients. Although the presence of autoantibodies should prompt liver biopsy to rule out coexisting autoimmune hepatitis, coexistence is exceedingly rare. Furthermore, the presence of autoantibodies has not consistently predicted worse histologic disease. Approximately 50% of NAFLD patients may have biochemical evidence for iron overload; however, hepatic iron content is usually not elevated, nor is it consistently associated with worse prognosis. In most cases, elevated ferritin represents nonspecific systemic inflammation caused by the metabolic syndrome and underlying insulin resistance rather than hemochromatosis. Fasting glucose and lipids, particularly triglycerides, may be elevated. Ceruloplasmin and α1-antitrypsin levels should be normal.

**RADIOLOGIC STUDIES**

After laboratory tests confirm the presence of hepatic disease, the liver is usually imaged to exclude common anatomic causes of enzymatic elevation, such as malignancy and biliary pathology. Ultrasonography, computed tomography, and magnetic resonance imaging may reliably diagnose fatty infiltration of the liver if the infiltration is greater than 33%. Therefore, negative imaging does not rule out NAFLD, but the presence of fatty infiltration in the appropriate clinical scenario is virtually diagnostic for NAFLD. Unfortunately, imaging is unable to differentiate steatosis from steatohepatitis, and thus liver biopsy is required if disease staging is necessary.
Liver biopsy is the gold standard in diagnosing NAFLD because histologic findings define the disease. In clinical practice, however, liver biopsy is not always required, and in fact, is controversial. Both the common histologic findings and clinical indications for liver biopsy are reviewed in this discussion.

**Histologic Findings**

Simple steatosis is characterized by the accumulation of predominantly macrovesicular fatty droplets, representing triglycerides, within the hepatocyte. The minimum required percentage of affected hepatocytes is greater than 5% to 10%.4

NASH consists of steatosis with varying combinations of hepatocellular injury, inflammation, and fibrosis.5 Typical lesions consistent with hepatocellular injury in NASH include cytologic ballooning of the hepatocyte with Mallory’s hyaline and, to a lesser extent, giant mitochondria, apoptosis, and necrosis.45,74 Cytologic ballooning is characterized by enlargement of the hepatocyte with rarefaction of the cytoplasm. Mallory’s hyaline is a ropey eosinophilic perinuclear inclusion found in these ballooned cells. Parenchymal inflammatory infiltrate is typically mild, more lobular than portal, and consists of a mixed population of cells consisting of neutrophils, lymphocytes, macrophages, and Kupffer cells.5 Fibrosis, when present, has a characteristic perisinusoidal/pericellular pattern.4 The most important feature of cirrhosis in NAFLD is that key histologic findings of both steatosis and NASH may become less conspicuous and even disappear altogether, making NASH an important cause of cryptogenic cirrhosis.5,75

Although the lesions of NASH are well described, there is no universally accepted criterion for the histologic diagnosis of steatohepatitis.5 A system for grading ongoing liver disease and staging fibrosis in NASH has been proposed.76 The histologic findings of pediatric NASH differ from findings in adults. In children, portal inflammation and fibrosis tend to be more prominent, whereas lobular changes such as hepatocyte ballooning, Mallory’s hyaline, and pericellular fibrosis may be less pronounced.5,77 A photomicrograph of the histologic findings in an adult with NASH is shown in the Figure.

**Clinical Indications**

The routine use of liver biopsy in patients with suspected NAFLD is controversial. Proponents of this practice note that only histologic staging determines prognosis. Opponents argue that because histologic findings do not change therapy, liver biopsy carries an unacceptable risk. Furthermore, opponents note that given the scope of disease, it is physically impossible to biopsy all affected individuals. Therefore, it seems prudent to compromise and biopsy patients only under selected circumstances.

The decision to biopsy must be tailored to the individual patient, and must be preceded by a discussion with the patient of the risks and benefits of the procedure. Patients in whom biopsy may be appropriate include the following: (1) patients with suspected NAFLD with a nondiagnostic noninvasive evaluation; (2) patients with evidence for fatty liver coexisting with a second disease, such as hepatitis C, hemochromatosis, or autoimmune hepatitis; (3) patients with noninvasive evidence of more advanced fibrotic disease; this latter group of patients should be biopsied for confirmation and referral for therapeutic clinical trials. Possible predictors of fibrosis include older age, the presence of the metabolic syndrome or its components, and an AST:ALT ratio greater than 1 or an ALT elevation greater than twice the upper limit of normal.36,37,49,56,52

**TREATMENT**

The main principles of treatment of NAFLD include correction of underlying risk factors, including obesity and insulin resistance; avoidance of factors that promote progression of liver disease; and specific treatment of NASH through pharmacologic treatments and
complementary and alternative medicines. Unfortunately, the US Food and Drug Administration has not approved medication for NAFLD; recommendations are based on existing literature and accepted clinical practice. Patients with fatty cirrhosis may require liver transplantation.

WEIGHT LOSS

Given the close correlations between NAFLD, obesity, and obesity-associated insulin resistance, prescribing weight loss is one of the most obvious treatments for NAFLD. Unfortunately, this “prescription” is often the least effective because most patients with NAFLD have struggled with obesity throughout their life and are unsuccessful at losing weight. Three primary approaches are available for addressing obesity in the setting of NAFLD: lifestyle changes, medication, and surgery.

Research addressing diet modification and exercise for weight loss in NAFLD is limited. Gradual weight loss of at least a 10% reduction in weight is the goal to improve serum transaminases as well as reduce hepatic steatosis, inflammation, and fibrosis on biopsy. Rapid weight loss, such as that which occurs with starvation diets, may actually worsen histopathology and is not recommended. Energy expenditure must exceed energy intake; therefore, dietary changes as well as increased physical activity should be prescribed. A careful history can reveal problem areas in a specific patient’s lifestyle, such as high consumption of fluids containing sugar. Obstacles to physical activity can be addressed including orthopedic, social, financial, and emotional barriers, and attempts should be made to overcome these issues. Some patients require a cardiovascular evaluation prior to initiating an exercise program. Current recommendations are at least 30 minutes of moderately intense physical activity at least 5 days per week.

Pharmacologic treatment of obesity has potential as a treatment for NAFLD in patients with a BMI greater than 30 kg/m². Orlistat, a reversible inhibitor of gastric and pancreatic lipases, is approved for weight loss and has been tried in NASH patients. A case series demonstrated that treatment with orlistat for 6 to 9 months showed significant improvement in both serum transaminases and histology. A 10-patient pilot study also demonstrated improvement in patients who achieved at least a 10% weight reduction. No controlled studies have been performed; use of orlistat, therefore, must be considered experimental.

Surgical treatment of obesity has been shown to result in histologic improvement in NASH (both in terms of inflammation and fibrosis) as well as improvement in the metabolic syndrome and certain factors (eg, cytochrome P450 2E1) that may play an etiologic role in the liver injury.

PHARMACOLOGIC TREATMENT

Both animal and human studies suggest a therapeutic role for “insulin sensitization” agents in NASH. Pilot studies support the therapeutic efficacy of metformin in humans. Several small pilot trials have evaluated the effects of the thiazolidinediones for the treatment of NASH and demonstrated improved biochemical, radiologic, and histologic features. The newer agents pioglitazone and rosiglitazone are now being studied in this setting, with initial positive results on liver enzymes and histology but the undesirable side effect of weight gain. Large multicenter trials of this class of agents have been initiated by the National Institutes of Health. Until these results are published, these drugs should not be used in routine clinical practice except when clinically indicated for type 2 diabetes mellitus.

The hepatoprotective agent ursodeoxycholic acid showed benefit for the treatment of NASH in a pilot study, however, a large multicenter trial did not show a significant improvement in the histologic grade or stage of NASH compared with placebo. This study had design flaws and the placebo group showed improvement; a multicenter study with a higher dose of this agent is underway.

Betaine is a drug that helps remove excess homocysteine and corrects abnormalities in the hepatic transmethylation pathway. A pilot study showed benefit, and a larger trial is underway.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Antioxidants are of particular interest in NAFLD because oxidative stress likely has a significant role in the development of NASH. Vitamin E is the most widely studied agent and is well documented to block stellate cell activation and collagen production in vitro and to block development of fibrosis in clinical models of liver disease. Initial clinical enthusiasm came from a pilot study by Lavine in 11 obese children, showing that vitamin E caused improvement in liver enzymes even without weight loss. Sanyal et al have recently reported beneficial effects on liver histology with the combination of vitamin E (400 IU) and pioglitazone (30 mg). Some concerns exist with high-dose vitamin E therapy, including increased mortality reported in a recent meta-analysis and possible interference with the efficacy of statin therapy for hyperlipidemia. Thus, hepatologists usually recommend use of high-dose vitamin E only in clinical trials until more information is available.
CONCLUSION

Owing to the obesity epidemic and rise of the metabolic syndrome, NAFLD has become the most common liver disease. The disease spectrum ranges from relatively benign steatosis to progressive fibrosis and cirrhosis, which may be complicated by hepatocellular carcinoma. The pathogenesis entails cytokine dysregulation, oxidative stress, and mitochondrial dysfunction superimposed on a background of overnutrition and insulin resistance, perhaps with genetic influences. The most common presentation is an obese patient with an asymptomatic transaminase elevation. Work-up involves a careful history, physical examination, laboratory evaluation, and imaging. A liver biopsy may be required for diagnosis, exclusion of coexisting liver diseases, and staging.

The treatment of NAFLD is rapidly evolving, and all patients should be counseled regarding lifestyle modifications that result in gradual weight loss with a goal of at least 10% weight loss. Patients who undergo bariatric surgery are likely to have improvement of liver disease with slow sustained weight loss. Insulin sensitizers and antioxidants are the most promising pharmacologic agents. No pharmacologic treatment is currently approved for treating NAFLD; however, several large studies are underway and may change treatment options in the near future.

REFERENCES