# Invited Review

## Nonalcoholic Fatty Liver Disease and Obesity

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**ABSTRACT:** Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognized medical condition that may progress to hepatic cirrhosis with liver failure. The pathologic picture resembles that of alcohol-induced liver injury, but it occurs in patients who do not abuse alcohol. NAFLD is more common among patients with evidence of insulin resistance. NAFLD refers to a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, fibrosis, and cirrhosis. The clinical implications of NAFLD are derived mostly from its common occurrence in the general population, specifically in obese individuals, and its potential to progress to cirrhosis and liver failure. It is difficult to propose a treatment strategy for NAFLD because its pathogenesis is poorly understood; however, the most commonly associated clinical features of obesity, diabetes mellitus, lipid disorders, and hypertension deserve therapeutic interventions independent of NAFLD. It is also not known if and how treatment of these other conditions affects the natural history of NAFLD, particularly in the long term.

Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease. The pathologic picture resembles that of alcohol-induced liver injury, but it occurs in patients who do not abuse alcohol.[1–5] NAFLD is more common among patients with evidence of insulin resistance, such as that observed in adults with obesity and type-2 diabetes mellitus.[1–12] However, with the rising prevalence of obesity in the population, NAFLD is even considered a significant health issue for obese children and adolescents.[13–15] Since NAFLD was first described by Ludwig and colleagues[1] in 1980, it has become increasingly recognized as a common condition that may occasionally progress to cirrhosis and liver failure. Other terminologies that were used for this disease entity include *pseudoalcoholic hepatitis*, *alcohol-like hepatitis*, *nonalcoholic Laennec's disease*, *fatty liver hepatitis*, *steatonecrosis*, *diabetic hepatitis*, and *nonalcoholic steatohepatitis* (NASH), the latter now being recognized as a distinct subset of NAFLD.[3,4] Recently, the abbreviation NAFLD was used to describe a wide spectrum of fatty liver diseases, ranging from simple steatosis (fat without inflammation, fibrosis, or other hepatocyte changes) to NASH (fat with hepatocyte changes, inflammation, and possibly fibrosis). Progression to advanced fibrosis and cirrhosis is thought to occur in the subset with NASH.[3–5] The diagnostic criteria for NAFLD continue to evolve and rely on a liver biopsy with the histologic finding of steatosis. Other findings that may be present include hepatocellular injury (portal or periportal inflammation, hepatocyte ballooning, Mallory hyaline bodies), and the pattern of fibrosis. Fibrosis often has a distinctive pericellular or "chicken wire" pattern before developing into confluent septae. Insulin resistance and oxidative stress have critical roles in the pathogenesis of NAFLD. No effective pharmacologic therapy yet exists for patients with NAFLD. However, lifestyle modifications, including weight reduction and exercise, may improve the spectrum of the disease. Liver transplantation remains a therapeutic alternative for some patients with decompensated end-stage liver disease, but NAFLD may recur after liver transplantation.[16]

### Epidemiology and Risk Factors

NAFLD is thought to be very common, and the prevalence of fatty liver of any degree in the general population is estimated to range from 13% to 18%.[17–19] Studies of liver biopsies of unselected autopsies or living donors for liver transplant indicate that the prevalence of NASH is less common and ranges from 2% to 4%.[20,21] NAFLD can affect any age group and is reported increasingly in the pediatric population, including 2.6% of children overall and up to 53% of obese children and adolescents.[22–24] The spectrum of histologic injury in this pediatric group clearly includes cirrhosis.[13] It is now suspected that there is an even distribution of NAFLD among men and women, although there may be gender variation among the specific classes. Series of patients with more advanced disease have generally

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had more women than men, suggesting that NAFLD in women takes a more aggressive course that it does in men.[25] Surveys have also suggested ethnic variation, with the disease being relatively uncommon among African Americans as compared with European and Hispanic Americans. This may represent variation in referral patterns, genetic differences in body fat distribution, or metabolic thermogenesis.[26–33] Clustering within kindreds also has been described, further suggesting that genetic factors predispose to the development of NAFLD.[34,35]

## Associated Conditions

The most common risk factor associated with NAFLD is the presence of the metabolic syndrome,[36] which is defined by the presence of 3 or more of the following criteria: (a) increased waist circumference, (b) hypertriglyceridemia, (c) hypertension, (d) high fasting glucose levels, and (e) a low serum level of high-density lipoprotein (HDL).

Therefore, NAFLD is now recognized to be the hepatic manifestation of the metabolic syndrome. However, it is important to note that all of the individual clinical components of the metabolic syndrome are strongly associated with obesity, and it is obesity itself that has the strongest association with NAFLD. Obesity is defined as a body mass index (BMI) $>30$ kg/m$^2$.[37] The more obese the patient, the greater the likelihood of fatty liver. Thirty percent of patients who are obese have fatty liver, as do up to 80% of morbidly obese patients (BMI $>35$ kg/m$^2$).[38,39] However, NAFLD is not confined to the obese. An increasing number of patients have been described who have a normal BMI, although these individuals may have central adiposity and occult insulin resistance.[3,5]

In addition to the association with the components of the metabolic syndrome described above,[3,5,36] NAFLD can also be associated with many other conditions (Table 1), including peroxisomal diseases, polycystic ovarian disease, mitochondrialopathies, Weber-Christian disease, jejunoileal bypass, Mauriac syndrome, Made-lung's lipomatosis, Wilson's disease, industrial solvent exposure, celiac disease, abetalipoproteinemia, and medications (including amiodarone, tamoxifen, perhexiline maleate, glucocorticoids, synthetic estrogens, calcium channel blockers, nucleoside analogs, and methotrexate).[3–5] Many of these disorders have in common either abnormal fat metabolism or mitochondrial injury or dysfunction. NAFLD can also be associated with hyperuricemia.

Table 1
*Causes of nonalcoholic fatty liver disease*

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| Clinical conditions |
| Metabolic syndrome (obesity, type 2 diabetes mellitus, hyperlipidemia hypertension) |
| Peroxisomal diseases |
| Polycystic ovarian disease |
| Mitochondrialopathies |
| Weber-Christian disease |
| Mauriac syndrome |
| Made-lung's lipomatosis |
| Wilson's disease |
| Industrial solvent exposure |
| Celiac disease |
| Abetalipoproteinemia |
| Medications |
| Amiodarone |
| Tamoxifen |
| Perhexiline maleate |
| Glucocorticoids |
| Synthetic estrogens |
| Calcium-channel blockers |
| Nucleoside analogues |
| Methotrexate |

## Pathogenesis

The pathogenesis of NAFLD remains incompletely understood, though many theories have been formulated to explain the observed sequence of events in the disease The critical feature in NAFLD associated with the metabolic syndrome is the presence of insulin resistance. It is still unknown why simple steatosis develops in some only some of the patients at risk and, furthermore, why steatohepatitis and progressive disease develops in others. A "2-hit" hypothesis has been proposed, whereby steatosis (first hit) sensitizes the liver to a variety of metabolic injuries (second hit) that lead to necrosis, inflammation, and fibrosis.[40,41] Differences in bodyfat distribution or host antioxidant systems, possibly in the context of a genetic predisposition, may be among the explanations.[3,5] The net retention of lipids within hepatocytes, mostly in the form of triglycerides, is a prerequisite for the development of NAFLD. The primary metabolic processes leading to lipid accumulation are not yet well understood, but probably relate to alterations of the pathways of uptake, synthesis, degradation, or secretion in hepatic lipid metabolism resulting from insulin resistance.[42] The molecular pathogenesis of insulin resistance seems to be multifactorial. Several molecular targets involved in the inhibition of insulin action have been identified and may serve as targets for therapeutic agents in the future. These include Rad (Ras associated with diabetes),[43] which interferes with essential cell functions (growth, differentiation, vesicular transport, and signal transduction); PC-1 (a membrane glycoprotein that has a role in insulin resistance),[44] which reduces insulin-stimulated tyrosine kinase activity; leptin,[45] which induces dephosphorylation of insulin-receptor substrate-1; fatty acids,[46] which inhibit insulin-stimulated peripheral glucose uptake; and tumor necrosis factor $\alpha$,[47] which down-regulates insulin-induced phosphorylation of insulin-receptor substrate-1 and reduces the expression of the insulin-dependent glucose-transport molecule GLUT4. Insulin resistance leads to fat accumulation in hepatocytes by 2 main

mechanisms: lipolysis and hyperinsulinemia.[3] Clinically significant amounts of dicarboxylic acids, which are potentially cytotoxic, can be formed by microsomal oxidation. This pathway of fatty acid metabolism is closely related to mitochondrial β-oxidation and peroxisomal β-oxidation. Deficiency of the enzymes of peroxisomal β-oxidation has been recognized as an important cause of microvesicular steatosis and steatohepatitis.[48] In particular, deficiency of acyl-coenzyme A oxidase disrupts the oxidation of very-long-chain fatty acids and dicarboxylic acids, leading to extensive microvesicular steatosis and steatohepatitis. Loss of this enzyme also causes sustained hyperactivation of peroxisome-proliferator-activated receptor-α (PPAR-α), leading to transcriptional up-regulation of PPAR-α-regulated genes.[48] PPAR-α has been implicated in promoting hepatic synthesis of uncoupling protein-2, which is expressed in the liver of patients with NAFLD.[49] Increased intrahepatic levels of fatty acids provide a source of oxidative stress, which may, in large part, be responsible for the progression from steatosis to steatohepatitis to cirrhosis. Mitochondria are the main cellular source of reactive oxygen species, which may trigger steatohepatitis and fibrosis by 3 main mechanisms: lipid peroxidation, cytokine induction, and induction of Fas ligand. Patients with steatohepatitis have ultrastructural mitochondrial lesions, including linear crystalline inclusions in megamitochondria. This mitochondrial injury is absent in most patients with simple steatosis and in healthy subjects.[50] Patients with steatohepatitis slowly resynthesize adenosine triphosphate (ATP) *in vivo* after a fructose challenge, which causes acute hepatic ATP depletion.[51] This impaired ATP recovery may reflect the mitochondrial injury found in patients with steatohepatitis.[50]

## Diagnosis

NAFLD is usually suspected in patients with asymptomatic elevations of serum aminotransferase levels, unexplained hepatomegaly, or the incidental discovery of findings suggestive of fatty liver on imaging studies.[3–8] However, the clinical presentation varies from patient to patient. Most are asymptomatic or have minimal, nonspecific complaints such as malaise or abdominal discomfort. Hepatomegaly, if present, is the only physical finding in most patients.[3–5]

Serum aminotransferase levels are elevated in >90% of patients with NAFLD.[3,7] These elevations are typically mild, usually 2–3 times the upper limit of normal.[3–5] The alanine aminotransferase (ALT) level is more elevated than the aspartate aminotransferase (AST) level, with an AST:ALT ratio of <1 (in contrast to alcoholic liver disease).[52] However, this ratio increases in the presence of fibrosis so it is usually not helpful in diagnosing NAFLD.[53] Serum concentrations of alkaline phosphatase and γ-glutamyltransferase are usually within normal limits or only slightly above the normal range. Other abnormalities, including hyperbilirubinemia, hypoalbuminemia, or a prolonged prothrombin time, may be found in patients with advanced cirrhosis.[3–5] Elevated serum ferritin and transferrin saturation are found in up to 50% of the patients; however, these often represent an acute-phase response to inflammation and not iron overload.[24,53] Although the hepatic iron index and hepatic iron levels are normal, some have suggested that heterozygosity for the hemochromatosis gene (HFE) gene may be increased in NAFLD and that accumulation of hepatic iron may lead to more progressive liver injury.[3,54] This remains to be confirmed. Low-titer antinuclear antibody positivity is present in up to 20% of patients with NAFLD but is nonspecific and probably not different from age- and gender-matched patients without fatty liver disease. Nonetheless, a liver biopsy should exclude autoimmune hepatitis as long-term management will differ.[4] Taken together, the clinical presentation and liver tests have poor predictive value with respect to histologic involvement.[3–5,55] Thus the confident diagnosis of NAFLD requires histologic confirmation in the absence of excessive alcohol intake; a daily intake as low as 20 g of alcohol in women and 30 g in men may be sufficient to cause alcohol-induced liver disease in some patients.[56] Other causes of elevated liver enzymes, including viral hepatitis, autoimmune responses, metabolic or hereditary factors, and drugs or toxins, should always be excluded, though these rarely present with hepatic fat.[3–5]

## Imaging Studies

Radiologic modalities such as ultrasonography, computed tomography, and magnetic resonance imaging may show increased fat accumulation (steatosis) in the hepatic parenchyma.[3–5] However, none of these imaging techniques can reliably detect hepatic fat content <25%–30%.[57] Furthermore, radiologic features of NAFLD may be nonspecific, leading to a significant variability in their interpretation between different radiologists. On ultrasonography, fatty infiltration of the liver produces a diffuse increase in echogenicity as compared with that of the kidneys, but steatosis can often not be distinguished from fibrosis.[57,58] Fatty infiltration of the liver produces a low-density hepatic parenchyma on computed tomographic scanning.[57] Steatosis is usually diffuse but occasionally is focal and can suggest the presence of a mass.[59] In such cases, magnetic resonance imaging can distinguish space-occupying lesions from focal fatty infiltration or sparing.[60] Magnetic resonance spectroscopy is a promising modality that allows a quantitative assessment of fat content in fatty liver.[5,61] Importantly, no imaging study can distinguish fat alone from steatohepatitis, and none are able to reliably identify or quantitate (stage) fibrosis.[57]

## Role of Liver Biopsy and Histology

The question of whether a liver biopsy is required in every person suspected of having NAFLD is

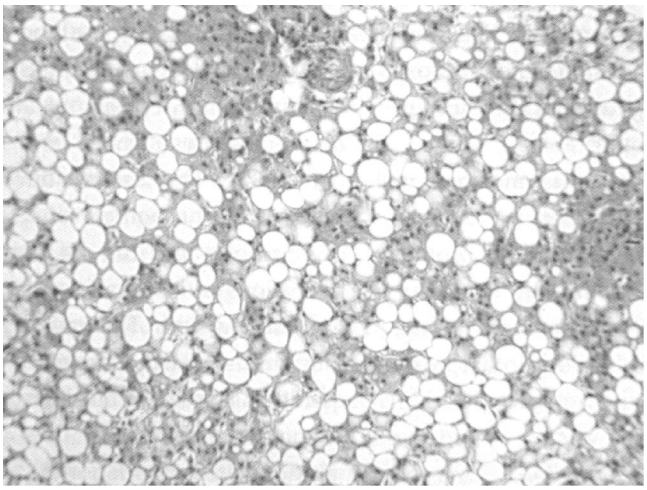

*Figure 1.* Liver biopsy histology: steatosis alone.

controversial. However, liver biopsy remains the gold standard and the best diagnostic tool for confirming and staging NAFLD.[3–5,57] It provides important prognostic information, and it may also be useful in determining the effect of medical treatment, given the poor correlation between histologic findings and laboratory tests or imaging studies.[3] Liver biopsy should be considered in patients with persistent elevation of serum aminotransferase levels regardless of whether treatment is considered, especially if the patient is obese or has diabetes mellitus.[4] The role the liver biopsy in assessing patients with liver abnormalities while using statin drugs has yet to be established; however, it is usually difficult to distinguish NAFLD from hepatotoxicity on clinical grounds in such patients. Interpretation and classification of liver biopsy findings in this disease are evolving. The degree of sampling error and the significance of occasional apoptotic bodies have not been studied adequately.[5] The histologic features of NAFLD may be indistinguishable from those of alcoholic fatty liver disease, and clinical correlation with careful history of alcohol consumption may be mandatory to distinguish between both groups.[3–5] Unlike other forms of chronic liver disease, no consensus currently exists regarding the grading and staging of NAFLD.[3–5,62] The grade indicates the activity of steatohepatitis (inflammation), whereas the stage reflects the degree of fibrosis. Figure 1 is a liver biopsy showing steatosis. Figure 2 illustrates steatosis with inflammation and ballooning of hepatocytes. Although the interobserver variability is relatively low in terms of diagnosing steatosis, cytologic ballooning, and perisinusoidal fibrosis, there is considerable variability with regard to the assessment of inflammatory changes.[62] A scoring system has been proposed by Brunt and colleagues[63] in which individual parameters indicative of necroinflammatory activity (cytologic ballooning, steatosis, and inflammation) are scored separately, and then a composite score is derived to indicate the grade of steatohepatitis. This approach also includes a staging system to assess hepatic fibrosis, which is composed of components for perisinusoidal fibrosis, portal fibrosis, and bridging fibrosis. A finding of fibrosis in NAFLD suggests more advanced and severe liver injury. According to a number of cross-sectional studies including a total of 673 liver biopsies,[1,3,24,53,62,64] some degree of fibrosis is found in up to 66% of patients with NASH at the time of diagnosis, whereas severe fibrosis (septal fibrosis or cirrhosis) is found in 25% and well-established cirrhosis is found in 14% of patients. Once cirrhosis develops, the amount of steatosis and cytologic ballooning may decrease or disappear completely, making the diagnosis difficult to make.[3–5,24,62] Many such cases are labeled as cryptogenic cirrhosis or "burned-out" NASH. In these settings, the diagnosis can only be suspected from the clinical profile of the patient and the presence of risk factors for NAFLD.[62,63]

## Natural History and Clinical Course

The natural history of NAFLD has not been well defined. The existing literature is almost entirely based on retrospective studies. An important study by Matteoni and colleagues[62] provided some assistance in predicting the clinical course of patients with NAFLD. In this study, subjects were grouped into 4 categories according to their initial liver histology as follows: (a) fatty liver alone; (b) fatty liver and lobular inflammation; (c) fatty liver and ballooning degeneration; (d) fatty liver and ballooning and Mallory's hyaline or fibrosis. The overall death rates over 18 years of follow-up were 33%, 30%, 26%, and 44%, respectively. Subjects in groups 3 and 4 had the highest number of liver-related deaths, and liver-related diseases were the second most common cause of death, with cancer being the first cause.

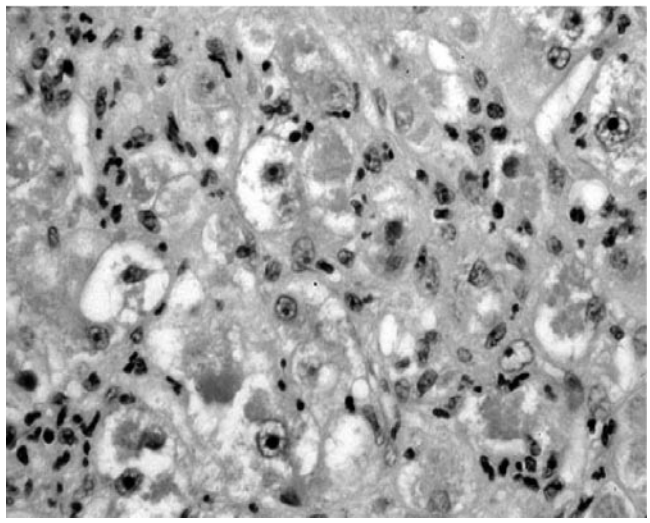

*Figure 2.* Liver biopsy histology: steatosis, inflammation, ballooning, and Mallory's hyaline.

Table 2
*Therapeutic strategies in the management of nonalcoholic fatty liver disease (NAFLD)*

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| Exercise and diet |
| Specific diets and bariatric surgery |
| Cytoprotective agents |
| Antioxidants |
| Iron reduction therapy |
| Antidiabetic and insulin sensitizing agents |
| Antihyperlipidemic agents |
| Liver transplantation |

The frequency and rates of progression from fat alone to steatohepatitis and fibrosis are not known. Risk factors for progression have also not been well described. However, cross-sectional studies suggest that age >40–50 years, degree of obesity, diabetes mellitus, or hyperlipidemia (especially hypertriglyceridemia) and a ratio of AST:ALT of 1 or greater are strong indicators of advanced stages of liver fibrosis.[17,53,65] The relatively increased prevalence of women among series with more advanced disease suggests that female gender may be a risk factor for progression, but this not a consistent finding in reported series.[3,24,25,53] A recent study by Fassio and colleagues[66] found that progression of fibrosis was present in one-third of NASH patients 4.3 years after the first liver biopsy, and obesity and BMI were the only factors associated with progression. Patients found to have pure steatosis on liver biopsy seem to have the best prognosis within the spectrum of NAFLD.[3,18] Other cross-sectional series have shown that 30% to 40% of patients have advanced liver fibrosis at the time of presentation,[24,67] whereas 10% to 15% of them may have established cirrhosis.[1,24,68] Three studies have found that patients with cryptogenic cirrhosis have a higher prevalence of diabetes, obesity, or both than those with cirrhosis from other causes, thereby suggesting that cryptogenic cirrhosis may represent burned-out NASH.[69–71] Furthermore, some patients who undergo liver transplantation for cryptogenic cirrhosis, develop steatosis or NASH in the graft during follow-up.[16,72]

Hepatocellular carcinoma has been reported in NASH patients, but the magnitude of this risk is not known.[73] Two large series of patients with hepatocellular carcinoma reported that 7%–13% of patients carried a diagnosis of cryptogenic cirrhosis and had a clinical phenotype of NASH.[74]

## Management

Resolution of histologic abnormalities as determined by liver biopsy remains the goal of treatment in patients with NAFLD. Common surrogate markers include normalization of serum aminotransferases and loss of fat as detected by radiologic imaging,[3–5,24] though these are probably insensitive as discussed above. Table 2 summarizes the therapeutic strategies in the management of NAFLD.

### *General Considerations*

It is not known whether alcohol use should be prohibited or restricted in patients with NAFLD. Lacking data, a pragmatic approach is to tailor this to the liver biopsy findings and recommend abstinence if either inflammation or fibrosis is present.[5] The concomitant use of medications that are associated with steatohepatitis as stated earlier requires weighing of the individual's risks and benefits. Certainly the benefits of controlling diabetes or hyperlipidemia exceed the small potential for hepatotoxity, and such therapy may even result in improvement of the liver disease (see below). An increasingly common but little-explored issue is workplace exposure to hydrocarbon solvents.[75]

### *Exercise and Diet*

Exercise and diet continue to be the cornerstones of therapy for NAFLD.[76] Although typically recommended together, the concept of the fit fat individual (ie, relatively well conditioned but obese) is relevant and suggests a benefit of exercise even in the absence of weight loss.[77] Exercise alters insulin sensitivity and substrate use in skeletal muscle, although only about one-third of patients achieve target levels of exercise[78,79] and obese individuals may be resistant to these changes.[80] A small number of studies of diet and exercise therapy have been reported in both adults and children. These typically demonstrate improvement of biochemical measures but variable changes in histology.[13,81–85] Histologic exacerbation has been observed when the rate of weight loss exceeds 1.6 kg per week. High-intensity exercise regimens are probably more effective in producing significant metabolic changes than low-intensity regimens or diet alone.[86]

### *Specific Diets and Bariatric Surgery*

The effects of many popular diets on hepatic steatosis are not known. A pragmatic approach is to recommend a reduced-calorie, balanced diet such as that endorsed by the American Heart Association or, as proposed by Spieth and colleagues in pediatric patients, the low-glycemic-index diet that emphasizes dietary composition.[87] Increased polyunsaturated fats (fish, flax seed oils) alter insulin sensitivity and prostaglandin metabolism, may increase uncoupling protein expression, and may promote lipid peroxidation, but the net effect in steatohepatitis is not known. Appetite-suppressing agents have lost favor due to their side effects. Recent data suggest a role for orlistat, a lipase inhibitor, as an adjunct to weight loss.[88] Several studies have reported beneficial effects of bariatric surgery, although precipitous weight loss has the potential to exacerbate steatohepatitis and may lead to liver failure.[38] Nevertheless, in those with complications of morbid obesity, bariatric surgery may prove to be first line therapy.[89–91] Outcome data of bariatric

surgery are still not well defined, but the number of procedures being done has increased exponentially in the past few years. The National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) currently is conducting a cooperative study of 6 centers to assess outcomes of bariatric surgery. Although there are no uniformly agreed-upon selection criteria for bariatric surgery, several basic inclusion and exclusion factors should be assessed. A liver biopsy before surgery is advisable. Older studies of the now abandoned jejunoileal intestinal bypass procedure supported a role for antibiotics and amino acid supplementation for patients who experienced decompensation.[92]

### *Cytoprotective Agents*

These agents combine an attractive safety profile, few drug interactions, and a plausible mechanism of action at the cellular or subcellular level. Ursodeoxycholic acid (UDCA) is a dihydroxy bile salt comprising 1% of the total bile salt pool and is both hepatoprotective and may have immunologic properties through NF$\kappa$B inhibition. UDCA has been suggested to be of benefit according to small, open-label studies.[93–96] However, a recent, prospective, multicenter, randomized, clinical study reported by Lindor and colleagues[97] reported that 2 years of therapy with UDCA at a dose of 13–15 mg/kg/day was no better than placebo for patients with NASH. Although safe and well tolerated, this treatment did not improve either liver biochemistries or histology compared with that of untreated controls.[97] Many clinicians continue to use this compound in clinical practice due to its benign side effect profile and the observation that liver chemistries sometimes improve.

### *Antioxidant Agents and Iron Reduction Therapy*

The suggestion that oxidative stress is involved in the pathogenesis of NASH has led to recent studies to examine to potential role of antioxidants in the treatment of NAFLD. Three studies have evaluated the effects of vitamin E in NASH patients. Two studies, one in children and one in adults, were uncontrolled, pilot trials. Lavine[98] demonstrated improvement in aminotransferase levels in children with NASH but did not evaluate the effect on histology. Hasegawa and colleagues[99] showed improvement in both hepatic inflammation and fibrosis in 5 of 9 NAFLD patients who lost weight and then were treated with vitamin E (300 mg/day) for 6 months. Recently, a prospective, randomized trial of vitamin E and vitamin C (1000 IU and 1000 mg, respectively) in 49 patients demonstrated a significant improvement in fibrosis in the vitamin-treated group. Diabetic patients with fibrosis seemed to have the greatest improvement.[100] The activated form of methionine, S-adenosyl-L-methionine (SAMe), is involved in several key hepatic metabolic pathways involved in gene expression and membrane fluidity and the generation of glutathione.[101] SAMe has been shown to reduce liver injury in several animal models. Betaine is a drug that serves as a methyl donor in the generation of methionine from homocysteine, increases SAMe levels, and would be anticipated to a similar effect. Indeed, betaine resulted in improvement in histology and serum aminotransferase levels in a pilot study of 10 NASH patients.[102] Silymarin, a popular milk thistle extract, is commonly used by patients with liver disease, though there are no published data to support its use in NAFLD.[103] Iron may increase oxidative injury. Serial phlebotomy for iron reduction in 17 patients with NAFLD and normal iron levels led to improvement in liver enzyme levels and insulin sensitivity in a small pilot study.[104]

### *Antidiabetic and Insulin-Sensitizing Agents*

Neither insulin therapy, sometimes recommended early in the course of type-2 diabetes, nor sulfonylureas have been adequately studied as treatment of fatty liver disease.[5] On the other hand, the thiazolidinediones have been studied and show promise.[105–107] These agents activate the PPAR-$\gamma$ nuclear transcription factor, alter skeletal muscle glucose uptake (through increased GLUT4 activity), decrease central adiposity, promote adipocyte differentiation, alter mitochondrial mass, and alter thermogenesis. The efficacy of troglitazone in lipodystrophy suggests a primary effect on lipid metabolism. Troglitazone was first used in NASH in a pilot study of 10 patients with results reported in 7, who completed up to 6 months of therapy. In these patients, both liver enzymes and histology improved.[105] This drug was removed from the market due to hepatotoxicity risk but set the stage for other compounds in the same class to be evaluated. Studies with pioglitazone and rosiglitazone have shown favorable outcomes. Thirty patients were treated with rosiglitazone 4 mg twice daily.[106] Of these 30, 22 had biopsy-proven NASH; in paired biopsies, 45% had significant improvement of the steatohepatitis. Unfortunately, the most common adverse event was weight gain, which occurred in two-thirds of the group. In an intriguing study of 18 nondiabetic NASH patients, 30 mg of pioglitazone daily led to significant histologic improvement in two-thirds, but again weight gain was common.[107] These studies highlighted the importance of treating insulin resistance as part of the therapeutic model for NASH, even if overt diabetes does not exist. Similarly, metformin has undergone limited study in NAFLD.[108–111] It down-regulates hepatic gluconeogenesis and also appears to divert fatty acids from triglyceride production to mitochondrial $\beta$ oxidation. In a pilot study of 20 humans with presumed NASH, metformin (500 mg 3 times a day for 4 months), was compared with 6 controls. Mean aminotransferase levels improved and even normalized in half of the actively-treated patients. Liver volume decreased by

20% and sensitivity to insulin improved. A limitation of that study was the lack of histologic information.[111] Other candidate agents include acarbose (an $\alpha$-glucosidase inhibitor), acipimox (inhibits lipolysis), and D-chiro-inositol.

### *Antihyperlipidemic Agents*

The role of treating hyperlipidemia in NAFLD is not yet clear. The general goal of therapy is to reduce triglycerides levels to below 150 mg/dL and to decrease serum low-density lipoprotein cholesterol levels to below 100 mg/dL, and even below 70 mg/dL if possible. This is best achieved using hydroxymethylglutaryl coenzyme A (HMG-CoA)-reductase inhibitors, or statin drugs. Atorvastatin, an HMG-CoA reductase inhibitor, resulted in improvement in biochemical and histologic parameters in a small pilot study.[112] However, a recent report showed no significant histologic differences between controls and patients with other various statin drugs.[113] Recent reports of subclinical skeletal muscle toxicity characterized by formation of ragged red fibers and mediated by mitochondrial injury are justifiable cause for concern for the use of these drugs in NAFLD. Liver enzymes should be monitored on a regular basis while patients receive statin therapy. Fibrates alter lipoprotein metabolism through the PPAR-$\alpha$ receptor, but early studies demonstrated no benefit.[93] However, bezafibrate showed benefit in tamoxifen-associated steatohepatitis.[114] Basaranoglu and colleagues[115] showed improvement in liver enzyme levels in patients treated with gemfibrozil, but histology was not measured.

### *Liver Transplantation*

Patients with liver failure from NAFLD are often poor candidates for transplantation due to comorbid conditions such as obesity, coronary artery disease, hypertension, and complications of diabetes. Both recurrence of NAFLD in patients with previously established NAFLD and *de novo* occurrence of NAFLD after transplantation for cryptogenic cirrhosis have been reported.[16,116] Progression to cirrhosis may develop in some patients who develop NAFLD after liver transplantation, but predictive factors have not been identified and treatment has not been studied in this setting. Immunosuppression, particularly the use of corticosteroids, could play a role in recurrence and progression due to the promotion of fatty liver and diabetes. Cyclosporine might promote fatty liver disease through direct effects on mitochondria.[117]

## Summary and Future Trends

There is currently no effective therapy for NAFLD, although several agents show promise in early studies. However, it is likely that new therapeutic targets will become available as our understanding of the pathogenesis of this disease evolves. For the present time, rigorous control of risk factors for NAFLD such as obesity, diabetes, and hyperlipidemia seems appropriate. Lifestyle modifications, including weight reduction and steady regular exercise, may improve the spectrum of the disease. Currently, with the possible exception of vitamin E, pharmacotherapy for NAFLD should be undertaken in the setting of clinical trials to assess the efficacy of therapy in a formal fashion. There remain insufficient data to justify the use of insulin-sensitizing agents in patients with insulin resistance but no diabetes. However, such therapies may be shown to be useful if ongoing clinical trials confirm a benefit. Other agents that have not been studied, including antihypertensive agents such as angiotensin II receptor blockers or probiotics to reduce bacterial endotoxin levels, seem possible. Additionally, the combination of specific diets that improve insulin resistance, coupled with pharmacotherapy to reduce oxidative stress and improve insulin, might be an attractive option.

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