Approach to the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) increasingly is recognized as a common cause of chronic liver disease in the United States. NAFLD spans a spectrum of clinicopathologic entities from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. Although the pathogenesis is not defined clearly and is being investigated actively, it is believed that insulin resistance plays a predominant role. In fact, some experts suggest that NAFLD should be considered the hepatic manifestation of the insulin resistance or metabolic syndrome [1]. To formulate an approach to the diagnosis and treatment of NAFLD, it is important to understand its epidemiology, clinical features, natural history, and pathogenesis.

Epidemiology

The epidemiology of NAFLD has been a subject of great interest among clinical investigators. With the epidemic of obesity and diabetes in the United States and worldwide, it is expected that the prevalence of NAFLD likewise will increase [2]. There are several limitations to the study of the epidemiology of NAFLD. First, there is no accurate noninvasive and sensitive marker for NAFLD. A liver biopsy is invasive and cannot be used as a screening test. Liver
enzymes can be normal in patients with NAFLD, and significant liver disease can be seen in those with NAFLD and normal liver enzymes \[3,4\]. Hepatic imaging lacks sensitivity for minor amounts of steatosis (ie, less than 33% of hepatocytes) \[5\]. Neither liver enzymes nor hepatic imaging can differentiate between various types of NAFLD (ie, simple steatosis versus NASH) \[4,5\]. Secondly, if liver enzymes are to be used, there is no consensus on which enzyme or combination of enzymes to use. The cut-off for abnormal values remains undefined \[6\]. These limitations result in varying estimates of prevalence rates for NAFLD in various studies. There are no data for the incidence of NAFLD.

In unselected populations, the prevalence of NAFLD has been estimated to be between 3% and 23% \[7–9\]. These estimates come from data from National Health and Nutrition Examination Survey III. The wide variation in prevalence rates results from the different enzymes or combination of enzymes and the different cut-off levels used to define NAFLD. In other parts of the world, prevalence estimates of NAFLD range from 9% to 36.9% \[10–16\]. The prevalence of NASH, a subtype of NAFLD, is even more difficult to define. In autopsy and liver biopsy series, the prevalence of NASH ranges from 1.2% to 6.3% \[11,17,18\].

The prevalence of NAFLD also has been evaluated in selected populations. In patients with diabetes mellitus, the prevalence of NAFLD can be as high as 63% \[19\]. In patients with abnormal liver enzymes in the absence of serologic or biochemical markers of liver disease, the prevalence of NAFLD ranges from 66% to 90%, and the prevalence of NASH is 34% to 40% \[20,21\]. In overweight patients and in obese patients undergoing bariatric surgery, the prevalence of NAFLD ranges from 72% to 93%; the prevalence of NASH ranges from 12% to 25% \[3,22–25\]. An incidental finding of cirrhosis was noted in up to 2% of patients in the bariatric surgery series. This is most likely an underestimation, because patients with any clinical or laboratory evidence of cirrhosis usually are excluded from bariatric surgery \[3,22–26\].

**Risk factors**

The main risk factors associated with NAFLD are obesity, diabetes mellitus, hyperlipidemia, and the metabolic syndrome. In many case series of patients with NAFLD, obesity, diabetes mellitus, and hyperlipidemia were observed in up to 93%, 55%, and 92% of patients, respectively \[27–35\]. Obesity, diabetes mellitus, and hyperlipidemia are components of the metabolic syndrome. Many experts believe that NAFLD is the hepatic manifestation of the metabolic syndrome. Most patients who have NAFLD have underlying insulin resistance, and many patients who have NAFLD fulfill criteria for the metabolic syndrome \[34–37\]. In one study, patients who had NASH were more likely than patients who had simple steatosis to fulfill criteria for the metabolic syndrome (88% versus 53%) \[35\]. In another study, 87% of patients who had NASH fulfilled criteria for the metabolic syndrome \[34\]. There are other causes of NAFLD, such as medications, jejunoileal bypass, and prolonged total parenteral nutrition.
NAFLD caused by these conditions has been called secondary NAFLD to differentiate them from NAFLD associated primarily with insulin resistance [38].

**Clinical features and natural history**

**Clinical manifestations**

Symptomatic disease is uncommon in patients with NAFLD, unless advanced liver disease is present. Some patients may report fatigue and right upper quadrant discomfort [28,30,31]. Hepatomegaly may be noted on physical examination [27,29–33]. Patients with advanced liver disease may present with the usual manifestations of end-stage liver disease such as jaundice, muscle wasting, or ascites. Most patients by definition do not drink significant amounts of alcohol. Although there is tremendous variability among reports on what constitutes insignificant alcohol intake, a level of two drinks a day was suggested as a cut-off at a recent conference [39].

Aside from abnormalities in serum glucose, cholesterol, and triglyceride levels, abnormal liver associated tests frequently are noted in patients who have NAFLD. The most commonly reported abnormality is elevated serum aminotransferases, usually not more than 10 times the upper limit of normal [30–33]. Some patients may present with elevated levels of alkaline phosphatase or \( \gamma \)-glutamyltransferase [31–33]. Abnormalities in serum albumin and bilirubin levels are observed infrequently, unless advanced liver disease is present.

**Histology**

There is no consensus on the histologic criteria for NAFLD and for the subtypes included within the spectrum of NAFLD. Steatosis is considered significant when more than 5% of hepatocytes contain fat [40]. The minimum histologic findings in NASH include hepatic steatosis with mixed lobular inflammation and hepatocellular ballooning [39]. Other findings, such as perisinusoidal fibrosis, glycogenated nuclei, and Mallory hyaline, can be observed but are not always required for the diagnosis of NASH [39]. Many of these typical features may disappear once cirrhosis is established [30,41]. A grading and staging scheme was published recently, but this requires validation in other studies [42]. A proposed classification scheme of NAFLD sorting NAFLD into one of four conditions showed that the prognosis of NAFLD might depend on its initial histologic classification [32]:

- Type 1—fatty liver alone
- Type 2—fat accumulation and lobular inflammation
- Type 3—fat accumulation and ballooning degeneration
- Type 4—fat accumulation, ballooning degeneration, and either Mallory hyaline or fibrosis
Natural history

The natural history of NAFLD has been studied by retrospective cohort studies and prospective cohort studies with paired biopsies.

Historical cohort studies

An early series of patients with a relatively short mean follow-up period of about 4 years showed that progression to cirrhosis occurred in two patients (5%) \cite{29}. One patient (2.6\%) died from decompensated liver disease \cite{29}. This patient had cirrhosis at the time of diagnosis. In a larger cohort of patients with NAFLD identified from a pathology database with a longer follow-up, differential progression was reported according to the histologic type of NAFLD \cite{32}. Those who had NAFLD types 3 and 4, which were considered NASH, were more likely to die of liver-related causes compared with the other types of NAFLD over a mean follow-up of more than 8 years \cite{32}. Eleven percent of patients who had type 3 or type 4 disease died of liver-related causes. Liver-related deaths were as common as cardiovascular deaths and second only to cancer-related deaths in this cohort \cite{32}. NAFLD types 1 and 2 had a relatively benign course, an observation also found in a different study that followed patients with simple hepatic steatosis over 11 years and found no cases of progression to cirrhosis or liver-related deaths \cite{43}.

Prospective cohort studies with paired biopsies

In 30 patients from early reports who had paired biopsies with a follow-up ranging from 1 to 9 years, fibrosis progression was noted in 14 (47\%) patients with 6 (20\%) progressing to cirrhosis \cite{44}. More recently, larger and better-characterized cohorts of patients with NAFLD who have paired liver biopsies have been published \cite{41,45–47}. All studies except two included only NASH patients. These studies found that about a third of patients showed progression of fibrosis over a follow-up of 2 to 5 years. In the same period of time, two studies found that 9\% progressed to cirrhosis \cite{45,46}. The differences in the proportion of patients progressing to cirrhosis between the older and newer cohorts are not clear but may be related to patient selection. About 20\% of the patients showed regression of fibrosis. Whether this represents true regression or sampling error in the liver biopsy specimens is not entirely clear.

Nonalcoholic fatty liver disease and cryptogenic cirrhosis

In the United States, cryptogenic cirrhosis accounts for about 10\% of all liver transplants performed, and it is the second leading reason for liver transplantation after hepatitis C virus (HCV) infection among obese patients \cite{48,49}. Studies evaluating the natural history of NAFLD have shown that progression to cirrhosis can occur. It has been demonstrated that the evolution of NAFLD to cirrhosis may be accompanied by loss of the typical histologic features of NAFLD (ie, steatosis and inflammation), resulting in cryptogenic cirrhosis \cite{30,41}. Many
cases of cryptogenic cirrhosis thus may represent burned-out NAFLD. Several studies have evaluated the association between cryptogenic cirrhosis and NAFLD. Caldwell and colleagues compared the clinical and demographic characteristics of patients who had cryptogenic cirrhosis with those who had NASH and those who had other etiologies for cirrhosis [eg, HCV infection] [50]. They found that patients with cryptogenic cirrhosis resembled NASH patients more closely than those with HCV-related cirrhosis in that they were more likely to be female, obese, or have diabetes [50]. These findings were supported by other similar studies of patients with cryptogenic cirrhosis [48,51]. In these studies, authors reported that patients who had cryptogenic cirrhosis were on average 10 years older than those who had NASH, consistent with the notion that NASH can progress to cirrhosis over a decade or so [50]. Another line of evidence providing support to the fact that most cases of cryptogenic cirrhosis represent burned-out NASH comes from post-transplant follow-up of patients receiving hepatic allografts for cryptogenic cirrhosis. Several studies have demonstrated that recurrence of NAFLD occurs in the hepatic allografts of these patients [48,52,53]. This recurrence seemed to be associated with the recurrence of conditions related to the metabolic syndrome [48].

Long-term outcomes of nonalcoholic fatty liver disease: liver failure, hepatocellular carcinoma, and mortality

In chronic liver disease, liver-related morbidity and mortality result from the development of cirrhosis and its complications. There are no large-scale prospective studies following the outcomes of patients who have NASH-related cirrhosis. Several retrospective studies have attempted to address clinical course of NASH-related cirrhosis. In a review of liver transplant evaluations and transplantations in a large transplant center, NASH was identified as the cause in 2.6% of all referrals for evaluation and in 2.9% of all transplants [53]. This relatively low rate is most likely an underestimate, because the investigators only considered cirrhosis to be NASH-related if histological features of steatohepatitis were present. It is believed, however, that features associated with NASH can disappear with development of cirrhosis. Additionally, patients with NASH may not have been referred for liver transplant evaluation because of medical comorbidities primarily related to the metabolic syndrome, such as coronary artery disease, diabetes, and obesity. In a retrospective cohort study, patients with cryptogenic cirrhosis and obesity were compared with lean patients who had cryptogenic cirrhosis and with patients who had HCV-related cirrhosis [54]. Obese cryptogenic cirrhosis patients were found to have the same rate of liver failure and lower survival as patients with HCV-related cirrhosis [54]. In another study, however, survival was similar between patients who had NASH-related cirrhosis and those who had HCV-related cirrhosis [55]. Hepatocellular carcinoma (HCC) was not detected in patients with NASH-related cirrhosis followed over a median of 5 years [55]. The differences in the outcomes between the two studies may be related to the small sample sizes or the cutoff levels for alcohol use. Al-
though difficult to obtain, the duration of cirrhosis before diagnosis is likely important in these kinds of studies. In fact, in the former study, obese cryptogenic patients were significantly older than the HCV-infected patients [54].

The first reports of the association between NAFLD and HCC came from reports of persons with known NAFLD who developed hepatocellular carcinoma during follow-up [56–58]. Large-scale studies following patients who had NASH over extended periods for the development of liver failure or hepatocellular carcinoma are not available. There are, however, several studies that evaluate the association between NASH and HCC through their common association with cryptogenic cirrhosis. Bugianesi and colleagues reported recently that features suggestive of NASH were observed more frequently in patients who had HCC and cryptogenic cirrhosis compared with those who had HCC associated with viral- and alcohol-induced liver disease [59]. In a recent study that compared obese patients who had cryptogenic cirrhosis with patients who had HCV-related cirrhosis, Ratziu and colleagues found that hepatocellular carcinoma occurred at a similar frequency between the two groups [54]. They suggested that obesity-related cryptogenic cirrhosis have the same carcinogenic potential as HCV-related cirrhosis. In another study, Marrero and colleagues noted that cryptogenic cirrhosis was the second leading cause of HCC in a large series from a tertiary care center [60]. Additionally, they noted that half of the patients who had cryptogenic cirrhosis in their series had either histologic or clinical features of NASH. They estimate that NASH may account for at least 13% of the HCC cases in their series [60]. One study did not detect HCC among patients who had NASH-related cirrhosis after a median follow-up of 5 years [55]. Although the evidence is indirect, HCC should be considered in the spectrum of NAFLD. The carcinogenic potential of NAFLD is likely to be intermediate between those who have viral- or alcohol-induced liver disease and those who have autoimmune liver disease or metabolic diseases. Surveillance for HCC should be part of the management of patients who have cirrhosis from NAFLD.

Pathogenesis

Numerous studies have been undertaken to assess and evaluate the pathogenesis of NAFLD. Central to the pathogenesis of NAFLD is insulin resistance. Insulin resistance is demonstrated almost universally in patients who have NAFLD [34,37]. In one study including patients who had simple steatosis and those who had NASH, insulin resistance was associated with NAFLD, independent of body mass index (BMI) or glucose tolerance [61]. The same results were noted in another study, and in addition, the degree of insulin resistance appeared more pronounced in patients who had NASH [37]. Chitturi and colleagues noted that 98% of patients who had NASH in their series had insulin resistance [34]. Because insulin resistance can be demonstrated in patients who have simple steatosis and NASH, other events are believed to be operative in
the progression from simple steatosis to steatohepatitis to cirrhosis. These findings have given rise to the multi-hit hypothesis [62].

The first hit is fat accumulation in the hepatocyte. This is believed to be caused by insulin resistance by means of increased lipolysis and increased delivery of free fatty acids to the liver [63]. Other abnormalities that contribute to fat accumulation include decreased synthesis of apolipoproteins and microsomal transfer protein gene polymorphism, both conditions potentially leading to decreased export of triglycerides out of the liver [64,65]. The presence of hepatic steatosis is thought to then set the stage for the development of inflammation and liver cell injury that is characteristic of NASH. There are several factors or second hits that have been proposed. They include oxidative stress from reactive oxygen species produced in mitochondria [37] and by cytochrome P-450 enzymes [66,67]. The contribution of iron to oxidative stress in NASH is controversial [68,69]. Cytokines, in particular tumor necrosis factor α (TNF-α), have been implicated as second hits [70]. Insulin resistance and obesity, especially central obesity, contribute to the hepatocyte injury in NASH by means of free fatty acids, the levels of which are increased in NASH [37,61]. Increased levels of free fatty acids can lead to increased reactive oxygen species production through increased mitochondrial and peroxisomal free fatty acids oxidation [71]. Insulin resistance also can lead to upregulation of CYP2E1, which contributes to oxidative stress [66]. Fibrogenesis in NASH occurs by means of hepatic stellate cell (HSC) activation by oxidative stress and cytokines. Adipokines such as Leptin and resistin, which are elevated in NASH, may enhance fibrogenesis in NASH through its direct effect on HSC or its indirect effects on production of TGF-B in sinusoidal and Kupffer cells. Adiponectin seems to have a protective effect in patients with NAFLD [72,73].

Management

Diagnosis

NAFLD should be considered in any patient who has abnormal liver enzymes, hepatomegaly, or bright liver on ultrasound and presents with features of metabolic syndrome. It is, however, important to exclude other causes of chronic liver disease, especially alcoholic liver disease and HCV infection, both of which can lead to hepatic steatosis. Another important reason to exclude other causes of liver disease is that there is increasing evidence that the coexistence of NAFLD and another form of chronic liver disease, especially HCV infection, can lead to more severe liver disease [74–76].

Liver enzymes

Liver enzymes are not a sensitive marker for NAFLD, as some patients with NAFLD can present with normal liver enzymes in the presence of significant liver disease [3,4]. In bariatric patients undergoing liver biopsy, 58% of patients
with histologic NASH had normal alanine aminotransferase (ALT), and 76% of patients had normal aspartate aminotransferase (AST) [3]. In another study, the entire spectrum of NAFLD was noted in NAFLD patients with normal liver enzymes including NASH and cirrhosis [4]. When compared with age- and gender-matched NAFLD controls with abnormal liver enzymes, there were no differences in the proportion of patients who had NASH [4].

**Hepatic imaging**

Various radiologic modalities of hepatic imaging have been evaluated in NAFLD. These have included ultrasound, CT scan, MRI, and magnetic resonance spectroscopy [5,77]. Although most modalities of hepatic imaging can detect steatosis and thus provide support to the diagnosis of fatty liver disease, sensitivity decreases when the amount of fatty infiltration involves less than one third of hepatocytes [5]. Furthermore, a more significant limitation of radiologic imaging is its inability to distinguish between simple steatosis and NASH or to detect significant fibrosis [5]. The use of a novel technique to measure liver stiffness looks promising in detecting significant fibrosis in patients who have hepatitis C, but this has not been evaluated in patients who have NAFLD [78].

**Liver biopsy**

Histologic endpoints are important in therapeutic trials of NAFLD. The role of liver biopsy in NAFLD in routine clinical practice, however, has not been established. A liver biopsy can confirm the diagnosis of NASH and exclude other causes of liver disease. Additionally, a liver biopsy is the only technique to differentiate between simple steatosis and NASH, a distinction that has prognostic significance [32]. A liver biopsy, however, carries a finite risk of morbidity and mortality and is expensive. Moreover, in the absence of effective therapy for NAFLD, knowing the histology may not carry an immediate impact on the management of individual patients. Several studies have evaluated clinical predictors of NASH and advanced fibrosis [24,33,79]. Obesity, older age, and the presence of diabetes are associated with advanced fibrosis [33,79]. A raised ALT or an AST:ALT ratio greater than 1 also has been associated with advanced fibrosis; however, a recent study showed that only 26% of patients who had NASH-related cirrhosis had an AST:ALT ratio greater than 1 [33,55,79,80]. A reasonable approach to a patient who has suspected NAFLD in clinical practice is to consider a liver biopsy in patients who have evidence of metabolic syndrome and in those who have persistently elevated liver enzymes despite optimal management of associated metabolic conditions such as obesity, diabetes, or hyperlipidemia [2]. Certainly, liver biopsy should be considered in individuals with clinical clues suggesting advanced fibrosis (ie, unexplained thrombocytopenia, elevated bilirubin, or hypoalbuminemia).

**Predictors of nonalcoholic steatohepatitis, advanced fibrosis, or mortality**

Several studies have attempted to determine clinical predictors of NASH or fibrosis in patients suspected of having NAFLD. Such a panel of clinical criteria
that can predict which NAFLD patients may have aggressive disease or advanced fibrosis would be very helpful for prognosis and in determining which patients should be referred for a liver biopsy.

Most studies have had cross-sectional design. In a series of morbidly obese patients undergoing bariatric surgery, Dixon and colleagues found that insulin resistance, raised ALT, and the presence of hypertension were independent predictors of NASH [24]. Having two out of the three variables predicted the presence of NASH with a sensitivity of 80% and a specificity of 89% [24]. Whether these criteria can be extrapolated to less severely obese patients has not been determined.

In another cross-sectional study, Angulo and colleagues evaluated 144 patients who had NASH and found that age greater than 45 years, AST:ALT greater than 1, obesity, and the presence of diabetes were independent predictors of advanced fibrosis [33]. In fact, none of the patients who were younger than 45 years and who were nonobese and nondiabetic had advanced fibrosis [33]. Additionally, in a cohort of patients who had NAFLD with in-depth pathologic and clinical data, presence of hepatocyte ballooning and Mallory bodies were associated independently with advanced fibrosis. Higher AST/ALT ratio was shown to be associated with hepatic fibrosis [81]. In overweight persons, at least 50 years of age, BMI of at least 28 kg/m², ALT of at least 2 times the upper limit of normal, and serum triglycerides of at least 1.7 mmol/L were found to be associated independently with advanced fibrosis [79]. The presence of one or fewer variables had a negative predictive value of 100% for advanced fibrosis [79]. Dixon and colleagues found that hypertension, raised ALT, and a high C peptide level were independent predictors of advanced fibrosis in morbidly obese patients who had NAFLD [24].

Although cross-sectional studies have provided some insight in identifying predictors of NASH-related fibrosis, few longitudinal data are available. In one longitudinal study consisting of 103 patients with paired liver biopsies, diabetes, higher BMI, and lower initial fibrosis score at initial biopsy were associated with a higher rate of fibrosis progression [41].

Although histologic fibrosis is an important outcome for NAFLD, studies with long-term outcomes such as development of clinical cirrhosis, liver-related mortality, or overall mortality will be important to determine the true long-term impact of NAFLD on patients’ lives. There are no large scale prospective studies reporting long-term outcome data for patients who have NAFLD. In a historical cohort study, the outcome of 44 patients who had NAFLD with diabetes was compared with 88 patients who had NAFLD without diabetes. In this study, patients who had NAFLD and diabetes were more likely to develop cirrhosis, have higher liver-related mortality, and higher overall mortality when compared with nondiabetic patients who had NAFLD. In this study, markers of hepatic dysfunction were the only independent predictors of increased mortality [80]. This study adds to the current body of evidence that patients who have NAFLD and diabetes are at the highest risk for developing short-term and long-term adverse outcomes as measured by histologic, clinical, and long-term endpoints.
Treatment

Numerous interventions have been used to treat patients who have NAFLD. In general, these clinical trials are open-label pilot studies involving a small number of patients. Additionally, some of the earlier studies have failed to adhere to a strict pathologic protocol for the diagnosis of NASH and have reported only biochemical parameters as treatment endpoints. These shortcomings have led to a lack of strong evidence supporting any form of treatment for patients who have NAFLD (Table 1).

Generally, treatment modalities for NAFLD can be divided into those targeting components of metabolic syndrome (obesity, hyperinsulinemia, or insulin resistance/diabetes mellitus), those targeting oxidative stress, and those providing cytoprotection. The following paragraphs summarize these treatment studies, focusing mainly on fully published data.

Because obesity consistently has been associated with NAFLD, weight reduction has been one of the initial forms of treatment used for NAFLD. Weight reduction strategies for treatment of NAFLD can be divided into medical intervention (diet with or without exercise) and surgical interventions.

Medical intervention includes diet, exercise, or a combination of the two. There are four published articles addressing the effectiveness of diet with or without exercise for NAFLD treatment [82–85]. Those studies included 3 to 31 patients. Most of these studies have suggested that weight loss can be associated with biochemical improvement, and one study showed histologic improvement of steatosis, but worsening inflammation, in the subgroup that lost weight rapidly [84].

Recently, surgical interventions for obesity have become more popular. The current surgical procedures for obesity can be divided into two categories, restrictive surgeries or malabsorptive surgeries [86]. Restrictive surgeries (ie, Lap-band procedure and vertical banded gastroplasty) decrease the capacity of the patient’s stomach and limit the amount of food he or she can consume. On the other hand, malabsorptive surgeries (ie, roux-en-Y gastric bypass and duodenal

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<td>Enzymes</td>
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<td>Enzymes, histology</td>
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switch procedures) bypass a large portion of patient’s small intestine, thus preventing the absorption of fats and other nutrients.

Weight reduction surgery has been shown to improve diabetes, hyperlipidemia, and hypertension. A recent study from the Swedish Obese Study Group randomized obese patients into two groups, weight reduction surgery (ie, bariatric surgery) or a conventional weight loss group [87]. This study suggests that bariatric surgery can be associated with better long-term outcomes in terms of cardiovascular risk factors, such as diabetes, hypertriglyceridemia, and hypertension [87].

Recent surgical techniques for obesity also have focused on issues related to NAFLD. In a recently published study, Dixon and colleagues examined the effect of weight reduction in patients who had NASH and underwent laparoscopic adjustable gastric banding (LAGB), a procedure that can lead to weight loss without altering the structure and function of the gastrointestinal system [88]. Thirty-six patients underwent two liver biopsies, one at the time of the initial surgery, and the other at the time of their second laparoscopic surgery or during a follow-up visit. At the enrollment, 23 patients fulfilled the pathologic criteria for NASH, but after losing $34 \pm 17$ kg, only four patients fulfilled the same criteria, suggesting that NASH resolved in 82% of these patients [88]. Similarly, 18 patients had a fibrosis score of two or more at the time of enrollment, while only three had a score of two or more at the end of the study [88]. Patients who had metabolic syndrome showed a greater improvement in liver histology with weight loss. This study suggests that surgical weight loss may be associated with histologic improvement in patients who have NASH [88].

Another study by Kral and colleagues examined the histological effects of another surgical technique, biliopancreatic diversion, on NAFLD [89]. Two liver biopsy specimens were obtained from two different groups of patients. The first group consisted of 11 patients who demonstrated cirrhosis on their initial biopsy and underwent multiple repeat biopsies. The second group of 104 patients underwent a second liver biopsy during reoperation. Of these 104 patients (each lost an average of $38 \pm 18$ kg over $41 \pm 25$ months after surgery), 28 of them showed a decrease in their fibrosis score; 42 exhibited new fibrosis, and 34 showed no change in their fibrosis score. Fibrosis improved in patients with an initial grade of two to five, and worsened in patients with initial grade of zero to one. Three patients developed new cirrhosis (two patients with an initial grade three fibrosis, and one patient with grade zero fibrosis). The study authors did not attribute the new fibrosis to the surgical procedure or to the rapid weight loss. They suggested that fibrosis was caused by other confounding conditions, including hemosiderosis, biliary obstructive disease, and recurrence of metabolic syndrome [89]. In the same study, 11 patients in group one with cirrhosis on the initial biopsy had sequential biopsies showing an overall decrease in their fibrosis score from a mean grade of five to a mean grade of three. Furthermore, eight patients who initially had cirrhosis and had a reoperation (they were included in the analysis of 104 patients) completely resolved their cirrhosis at reoperation [89]. This study provides
encouraging data regarding the positive impact of weight reduction surgery in patients with NASH.

Another important component of metabolic syndrome is diabetes and insulin resistance. As discussed previously, insulin resistance is a common characteristic of patients who have NAFLD. There are two general categories of treatment modalities targeting insulin resistance in patients who have NASH.

One strategy is to use metformin to improve hepatic insulin resistance. In a small study of 14 patients who had NAFLD, 500 mg of metformin was given three times a day for 4 months [90]. Although the study documented radiologic (ultrasound echogenicity) and biochemical improvements, histologic data were not available [90]. This report was followed by a study with a longer duration of follow-up [91]. Although there was an initial decrease in ALT and improvement in insulin sensitivity, this was not sustained to the end of the study [91]. Both studies noted that metformin was generally safe and well tolerated. The exact role of metformin in NAFLD requires further evaluation in randomized controlled trials.

Another approach to treatment of NAFLD is the use thiazolidinediones to improve insulin sensitivity and treat NASH. Caldwell and colleagues treated 10 patients with biopsy-proven NASH with troglitazone for 6 months [92]. In this study, serum aminotransferases normalized in seven patients by the end of the treatment period; the biochemical improvement was accompanied by mild histologic improvement [92]. Troglitazone has been withdrawn from the market because of potential for severe hepatotoxicity.

Two recently published studies evaluated the newer thiazolidinediones in NASH. Tetri and colleagues reported their data on 30 patients who had biopsy-proven NASH treated for 48 weeks with rosiglitazone at 4 mg twice a day. At the end of therapy, these patients showed improvements in insulin resistance and biochemical and histologic improvement [93]. Promrat and colleagues used pioglitazone in 18 patients (30 mg/d for 48 weeks) [94]. Similar to rosiglitazone, pioglitazone improved aminotransferases and histologic and radiologic endpoints [94]. In both studies, almost two thirds of patients gained some weight, and the biochemical abnormalities reversed after discontinuation of treatment. Despite encouraging data, randomized, placebo-controlled trials using these drugs are lacking.

Hyperlipidemia is another characteristic of metabolic syndrome commonly seen in patients who have NAFLD. Although several lipid-lowering agents have been used to treat NAFLD, most of the studies have reported only biochemical improvement [95–98]. In fact, in one study of patients who had hypertriglyceridemia, 12 months of clofibrate did not appear to render any significant benefit [95]. On the other hand, atorvastatin treatment for 1 year produced significant improvements in ballooning degeneration of hepatocyte and inflammation in seven patients who had NASH [97]. Furthermore, a randomized controlled trial of short-term gemfibrozil in 46 patients demonstrated a significant decrease in serum transaminases, but histologic data were unavailable [96]. Orlistat also has been shown to reduce weight and improve hyperlipidemia, thus leading to biochemical and histological improvement [99].
Given the theoretical role of oxidative stress in the pathogenesis of NASH, numerous studies have focused on the use of antioxidants for NAFLD treatment. The antioxidant compound Vitamin E has been evaluated in numerous studies for patients who have NASH. [100–103] Vitamin E may be beneficial, because it protects cellular structures against damage from oxygen free radicals and from reactive products of lipid peroxidation. In a pilot study involving 11 obese pediatric patients who had NAFLD, the dose of Vitamin E ranged from 400 to 1200 IU/d [100]. All 11 patients showed normalization of their liver enzymes [100]. In another study, Vitamin E (300 IU/d) was given to 12 patients who had NASH and 10 patients who had NAFLD for 12 months [101]. Liver enzymes were improved significantly when compared with baseline readings [101]. Despite this data, long-term efficacy and safety of Vitamin E are lacking.

Other potential antioxidant therapies for NASH include betaine, N-acetylcysteine, and pentoxifylline. Betaine, a metabolite of choline that increases S-adenosylmethionine levels, improved serum aminotransferases and liver histology in a small study of 10 patients who had NASH [104]. Biochemical improvement was reported in another small study investigating treatment with N-acetylcysteine given for 3 months [105]. Pentoxifylline (400 mg three times per day) was given to eighteen patients with biopsy-proven NASH for 6 months [106]. After 6 months of therapy, improvement in insulin resistance and biochemical values was documented.

Cytoprotective agent ursodeoxycholic acid (UDCA) also has been used to treat patients who have NASH. In one small open-label pilot study of 24 patients, UDCA (13 to 15 mg/kg/d for 48 weeks) suggested potential benefit to these patients, as reflected by improvements in serum aminotransferases and some improvement in hepatic steatosis [95]. This study was followed by a randomized controlled trial of 166 patients treated for 48 weeks with either a placebo or UDCA (13 to 15 mg/kg/d) [47]. This study showed that relatively low doses of UDCA used for treatment of patients who had NASH produced similar biochemical and histologic efficacy to placebo [47]. Trials using higher doses of UDCA or trials using UDCA in combination with other agents are not available.

Summary

NAFLD is a common cause of chronic liver disease. Most patients who have NAFLD present with conditions associated with the metabolic syndrome (ie, obesity, diabetes, and hyperlipidemia). This strong association has led to the suggestion that NAFLD should be considered the hepatic manifestation of the metabolic syndrome. The spectrum of NAFLD ranges from simple steatosis to NASH and cirrhosis. Hepatocellular carcinoma also is considered a complication of the advanced stages of this spectrum. The prognosis of NAFLD depends on the histologic type. Those who have simple steatosis usually have benign disease, and those who have NASH can have progressive liver disease. Even steatosis
alone, however, can aggravate other liver diseases such as chronic hepatitis C. The pathogenesis of NAFLD is the subject of intense investigation, but insulin resistance plays a predominant role. Although numerous agents have been used, there are no proven effective treatments for NAFLD. Nevertheless, interventions improving insulin resistance (surgical weight loss for morbidly obese patients, insulin-sensitizing agents for patients who have NASH) are promising. It is likely that future effective treatment for NAFLD may require two or more drugs or interventions. Studies using insulin-sensitizing agents and antioxidants are underway.

References


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