Digestive Diseases and Sciences, Vol. 50, No. 1 (January 2005), pp. 171–180 (© 2005)
DOI: 10.1007/s10620-005-1267-z

Nonalcoholic Fatty Liver Disease: A Clinical Review

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Nonalcoholic fatty liver disease may be the most common liver disease in the United States, with a high prevalence in the obese, type 2 diabetic population, and it is probably underestimated as a cause for cirrhosis. Clinicopathologically, it represents a wide spectrum of histologic abnormalities and clinical outcomes, ranging from benign hepatic steatosis to cirrhosis. Pathophysiologically, insulin resistance is thought to be pivotal in the development of steatosis, after which a second oxidative stressor produces lipid peroxidation and nonalcoholic steatohepatitis (NASH). Liver biopsy is the gold standard for diagnosis and prognosis. The need for an effective treatment is both clear and urgent, yet in the absence of proven therapies, treatment is directed toward weight loss and comorbidity management. For patients with NAFLD at risk of disease progression, there is a lack of large, randomized, placebo-controlled trials of adequate treatment duration, with baseline stratification according to histologic severity.

KEY WORDS: nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; insulin resistance; obesity; hyperlipidemia.

Nonalcoholic fatty liver disease (NAFLD) is a common clinicopathological condition characterized by significant lipid deposition in the hepatocytes of the liver parenchyma. The pathological picture bears a striking resemblance to that of alcohol-induced liver injury, but it occurs in individuals who deny a significant history of alcohol ingestion. NAFLD comprises a wide spectrum of liver damage, ranging from simple macrovesicular steatosis to steatohepatitis, advanced fibrosis, and cirrhosis (1). Subsets of NAFLD which progress to cirrhosis are being increasingly recognized as a major cause of liver-related morbidity and mortality with the potential to progress to liver failure. Significant research endeavors are being directed toward understanding the pathogenesis of NAFLD and designing therapeutic strategies. This article provides a clinical overview of NAFLD, focusing on its definition, epidemiology, etiopathogenesis, diagnosis, natural history, and treatment.

Manuscript received February 13, 2004; revised manuscript received June 10, 2004; accepted June 15, 2004.

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DEFINITION

In 1980, Ludwig and colleagues originally coined the term nonalcoholic steatohepatitis, "NASH," to describe the morphologic pattern of liver injury in 20 patients evaluated at the Mayo Clinic over a 10-year period (2). These patients had histologic evidence suggestive of alcoholic hepatitis on liver biopsy (i.e., steatosis and lobular inflammation) but no history of alcohol abuse. Many of these patients were female (60%) and the majority were obese (90%). Hyperlipidemia and diabetes mellitus were also frequently recognized comorbidities in this population. Several other terms have been used to refer to this entity, including pseudoalcoholic liver disease, alcohol-like hepatitis, diabetic hepatitis, nonalcoholic Laennec's disease, and steatonecrosis (3). However, seeing that the disease represents a spectrum of pathology, the umbrella term

"NAFLD," first introduced in 1986, became the preferred one (4). The spectrum ranges from simple benign fatty liver (hepatic steatosis) to NASH, characterized by fatty change with lobular inflammation, hepatocellular injury, and Mallory hyaline, progressive fibrosis, and cirrhosis, and has been defined both histologically and clinically. To date, only those with histologic evidence of steatohepatitis have demonstrated evidence of progression to fibrosis or cirrhosis (5).

EPIDEMIOLOGY

NAFLD has been reported worldwide but geographic variations in prevalence are evident. Although the worldwide prevalence has not yet been determined, it has been quoted as 10–24% in various populations (6). Although these estimates may reflect referral bias, NAFLD is estimated to be the most common liver disease in the Western world, and its prevalence is likely increasing. It affects all racial and ethnic groups and has no age or sex predilection. 2.6% of children are affected (7) and this figure increases to 22.5% (7) to 52.8% (8) in the obese child population. The significance of pediatric NAFLD has been borne out in a follow-up study for up to 16 years, where NAFLD was shown to have a progressive clinical course in some, and children should be closely monitored for the development of type 2 diabetes mellitus (9)

NAFLD is the cause of asymptomatic elevation of aminotransferases in 42–90% of cases once other causes of liver disease are excluded (10). The prevalence of NAFLD increases significantly, to 57.5% (11) to 74% (12), in obese individuals. In the United States it has been estimated that steatosis affects over two-thirds of the obese population (13, 14), whereas NASH is found in 19% of these obese individuals (13). Further, about one-third of the U.S. population suffering from type 2 diabetes mellitus have NAFLD. It is likely that the increasing prevalence of NAFLD in the United States and other developed countries parallels the surge of obesity and diabetes that has become evident among all age groups.

ETIOPATHOGENESIS

Many different agents and conditions have been associated with fatty liver disease. These may be due to acquired insulin resistance (the so-called "Syndrome X"), inborn errors of metabolism, medical conditions or surgeries associated with weight loss, and various drugs and toxins. Potential causes of NAFLD are listed in Table 1. It appears that NAFLD, diabetes mellitus, and hyperlipidemia share a similar pathogenesis. It is likely that steatohepatitis is mediated through insulin resistance, a common factor in all of these conditions (15). Recently, patients with hypothalamic/pituitary dysfunction, at risk of excessive weight gain,impaired glucose tolerance, and dyslipidemia, were also found to develop progressive NAFLD (16).

Table 1. Conditions Associated with Fatty Liver Disease

Acquired insulin resistance
Obesity
Diabetes mellitus
Hyperlipidemia
Hypothalamic–pituitary dysfunction
Genetic/inborn errors of metabolism
Abetalipoproteinemia
Weber–Christian disease
Galactosemia
Limb lipodystrophy
Type 1 glycogen storage disease
Wilson's disease
Tyrosinemia
Systemic carnitine deficiency
Refsum's syndrome
Nutritional/intestinal
Surgical
Jejunoileal bypass
Gastroplasty for morbid obesity
Biliopancreatic diversion
Extensive small bowel resection
Total parenteral nutrition
Rapid weight loss
Starvation and cachexia
Protein calorie malnutrition: marasmus and kwashiorkor
Inflammatory bowel disease
Jejunal diverticulosis with bacterial overgrowth
Drugs and toxins
Amiodarone
Methotrexate
Tamoxifen/synthetic estrogens
Glucocorticoids
Nucleoside analogs
Calcium channel blockers
Perhexiline maleate
Phosphorus
Organic solvents
Petrochemicals
Dimethylformamide
Rapeseed oil

Although the exact pathogenesis of NAFLD remains poorly understood, the prevailing hypothesis by experts in the field is that several insults or "hits" are involved in causing progressive liver injury (17). With the initial hit, macrovesicular steatosis results. Insulin resistance (7) most likely plays a central role in the net retention of lipids, particularly triglycerides, within the hepatocytes (18). Although the mechanisms have not been completely elucidated, this is thought to result from decreased disposal

of fatty acids due to impaired mitochondrial β-oxidation (18). The second hit is generally attributed to oxidative stress, which causes peroxidation of lipids in the hepatocyte membrane (17), cytokine production, and Fas ligand induction (19) and is in large part responsible for the progression from steatosis to NASH to cirrhosis. Bacterial toxins (20), overproduction of cytokines (especially tumor necrosis factor-α) (21), and alteration of hepatocyte ATP stores and cytochrome P450 Cyp2E1/Cyp4A enzyme activity (22) are also putative triggers for disease progression and fibrogenesis. The role of leptin in NASH is controversial. One study suggested that increased serum leptin may promote hepatic steatosis and steatohepatitis (23), while another study concluded that leptin levels correlate directly with severity of hepatic steatosis but not with inflammation or fibrosis (24). The role of iron (which can lead to stellate cell activation and collagen deposition) in the pathogenesis of NAFLD remains uncertain (25).

DIAGNOSIS

Symptoms

As with many other types of chronic liver disease, most patients with NAFLD (48–100%) (26–28) are asymptomatic. The liver disease is often discovered incidentally during routine laboratory examination when a hepatic panel reveals an elevated ALT level (2). NAFLD is the most common cause for unexplained persistent elevation of ALT levels once hepatitis C and other chronic liver diseases have been excluded (29). When symptoms occur they are usually nonspecific. Vague right upper quadrant abdominal pain, fatigue, and malaise are the most common of these nondescript symptoms (18). Rarely, pruritus, anorexia, and nausea may develop. Jaundice, abdominal distension (ascites), gastrointestinal bleeding, and confusion (encephalopathy) are all indicative of advanced liver disease (decompensated cirrhosis), occurring late in the course (30).

Signs

There are no pathognomonic signs of NAFLD. Obesity is the most common abnormality on physical examination, occurring in 30–100% of patients in various cross-sectional studies (2, 26, 28). Hepatomegaly has been reported in up to 75% of patients in several studies (2, 27). The prevalence of hepatomegaly may increase to 95% when assessed by ultrasonography. Stigmata of portal hypertension appear to occur less frequently, although splenomegaly was noted at the time of diagnosis in 25% of patients in one study (2). Of the various stigmata, spider nevi and palmar erythema are the most common (27). Muscle wasting may occur as liver disease becomes more advanced but is often underestimated due to edema and preexisting obesity (30).

Laboratory Findings

Mild to moderate elevation of serum aminotransferases (ALT and AST) is the most common and often the only laboratory abnormality found in patients with NAFLD (1). There is no significant correlation between the degree of serum aminotransferase elevation and the histologic severity of hepatic inflammation or fibrosis (27, 31, 32). Unlike those with alcohol-induced steatohepatitis, who typically manifest disproportionate increases in the AST level relative to the ALT level, patients with NAFLD usually have an AST/ALT ratio <1 (2, 27, 28). The AST/ALT ratio tends to increase with the development of cirrhosis, thus losing its diagnostic accuracy (31). Serum alkaline phosphatase (26, 33) may also be slightly elevated in about one-third of patients. Hyperbilirubinemia, hypoalbuminemia, and prolongation of the prothrombin time are noted infrequently and generally only seen once liver failure has become established. Elevated serum lipid profiles and glucose concentrations are also common in NAFLD patients, reported in 25 to 75% of cases (3).

A small percentage of patients with NAFLD may have a low-titer ($\leq$1:320) antinuclear antibody (ANA) positivity (2, 34). The role of iron in the pathogenesis of NAFLD remains controversial. Bacon *et al*. first reported that many patients with NASH had biochemical evidence of iron overload (26). Several series have shown an elevation of transferrin saturation (in 6–11%) and serum ferritin level (in approximately 50%), however, the hepatic iron index is consistently <1.9 (26, 31). The significance of HFE mutations in NASH remains to be fully established. Whether the presence of iron overload is associated with increased hepatic fibrosis in NASH is also a controversial issue (25, 35). The available data do not support routine screening for genetic hemochromatosis in patients with NASH (18).

It is important to exclude secondary causes of hepatic fat so that the diagnosis of primary NAFLD can be made reliably. Hepatitis C (HCV) (27) and alcoholic liver disease are particularly important because of the high prevalence of these two hepatotoxic agents. HCV can cause histologic changes that closely resemble NAFLD (36), thus serologic testing to exclude viral hepatitis has become a prerequisite for the diagnosis of NAFLD. By its very definition, the diagnosis of NAFLD cannot be made in the setting of excessive alcohol consumption. However, there is no consensus among investigators concerning what is an excessive amount of alcohol and thus there are no published and universally accepted threshold levels. It is generally believed that a fatty liver does not develop with alcohol

consumption levels <20 g/day in females and 30 g/day in males. In a prospective study of the impact of moderate alcohol consumption on steatosis in patients with chronic HCV, the proportion of patients with moderate or marked steatosis increased gradually with the level of alcohol intake (37). Assessment of the amount of alcohol consumed from that reported by patients is notoriously inaccurate (30). Random blood alcohol level measurements are one method advocated to determine the extent of alcohol consumption, but these may be difficult to obtain (38). Several surrogate markers for chronic excessive alcohol intake have also been evaluated. These include serum GGTP levels (39), mean corpuscular volume (39), AST levels, AST/ALT ratio (40), mitochondrial AST levels (41), and desialylated transferrin levels (42). Most of these have poor sensitivity and specificity, and neither negative or positive predictive values are high enough to be of clinical utility. The ratio of desialylated to total transferrin appears to be the most promising of these surrogate markers (43).

Imaging Studies

Several noninvasive imaging techniques, including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), can identify hepatic steatosis and have been advocated as diagnostic tests for NAFLD. Of these, US is the least expensive. The sonographic findings of diffuse fatty change include a diffuse hyperechoic echotexture (bright liver), increased liver echotexture compared with the kidneys, vascular blurring, and deep attenuation (44). Fatty infiltration of the liver produces a low-density hepatic parenchyma on CT scanning (45). In a direct comparison of CT with US, US was found to be more sensitive in detecting fatty change (46). However, when fatty change is patchy or focal, CT scan and MRI are superior to US (47). Also, when a semiquantitative assessment is required or when multiple comparative studies are planned over time, CT is superior to US (30). Magnetic resonance spectroscopy is a newer innovative radiologic technique allowing one to examine the resonance frequencies of all proton species within a region of interest and is being investigated as a means of obtaining a more quantitative assessment of fatty liver infiltration (48). Despite the utility of these imaging modalities in the diagnosis of diffuse fatty disorders of the liver, none is sufficiently sensitive to detect hepatic inflammation, fibrosis, or cirrhosis. In a prospective study evaluating the role of different radiological modalities in establishing the diagnosis of NASH, neither US, CT, nor MRI was able to detect the presence of hepatocyte ballooning, Mallory's hyaline, or fibrosis, which are all important features in the diagnosis of NASH (49). With the inability to distinguish simple steatosis from steatohepatitis and stage the severity of injury, liver biopsy remains the best diagnostic test for steatohepatitis (NASH).

Liver Histology

The value of liver biopsy for diagnosing NASH in clinical practice is a hotly debated topic. The lack of effective medical therapy for NAFLD and risks associated with biopsy are arguments proposed against obtaining tissue sampling (30). Nevertheless, liver biopsy is the only accurate method for the diagnosis of NASH and the only means to determine the severity of liver damage and long-term prognosis. Angulo *et al*. identified independent predictors of liver fibrosis that may help in identifying patients in whom a liver biopsy may provide the most prognostic information. These include an age >45 years, the presence of obesity or type 2 diabetes mellitus, and an AST/ALT ratio >1 (31). Both the decision to perform a liver biopsy in clinical practice and the timing of the biopsy must be individualized and should include the patient in the decision-making process (30). An algorithmic approach to the diagnosis and workup of NAFLD is presented in Figure 1.

The histological features of NAFLD are indistinguishable from those of alcohol-induced liver disease. There are two lesions associated with NAFLD: (i) predominantly macrovesicular steatosis alone or (ii) predominantly macrovesicular steatosis and varying amounts of cytologic ballooning and spotty necrosis, scattered mixed neutrophilic–lymphocytic inflammation, glycogen nuclei, Mallory's hyaline, and perisinusoidal fibrosis (NASH). All of the features of steatohepatitis are not present in every instance of steatohepatitis. The severity of steatosis can be graded on the basis of the extent of involved parenchyma. Brunt's classification (reported in Table 2) is a system that unifies the steatotic and necroinflammatory lesions into a "grade" and the types of fibrosis into a "stage" (50). More recently, a NASH Clinical Research Network has been formed, which is a multicenter consortium sponsored by the NIDDK to study the natural history of, and initiate clinical therapeutic trials for, NAFLD and NASH. To have a unified histologic evaluation in the planned studies, pathologists from eight participating centers designed and validated a histologic scoring system for the spectrum of NAFLD that has inter- and intrarater agreements similar to those of other semiquantitative systems for chronic liver disease (51).

NATURAL HISTORY

The natural history of NAFLD is ill-defined, but it seems to be determined by the severity of histologic damage (1).

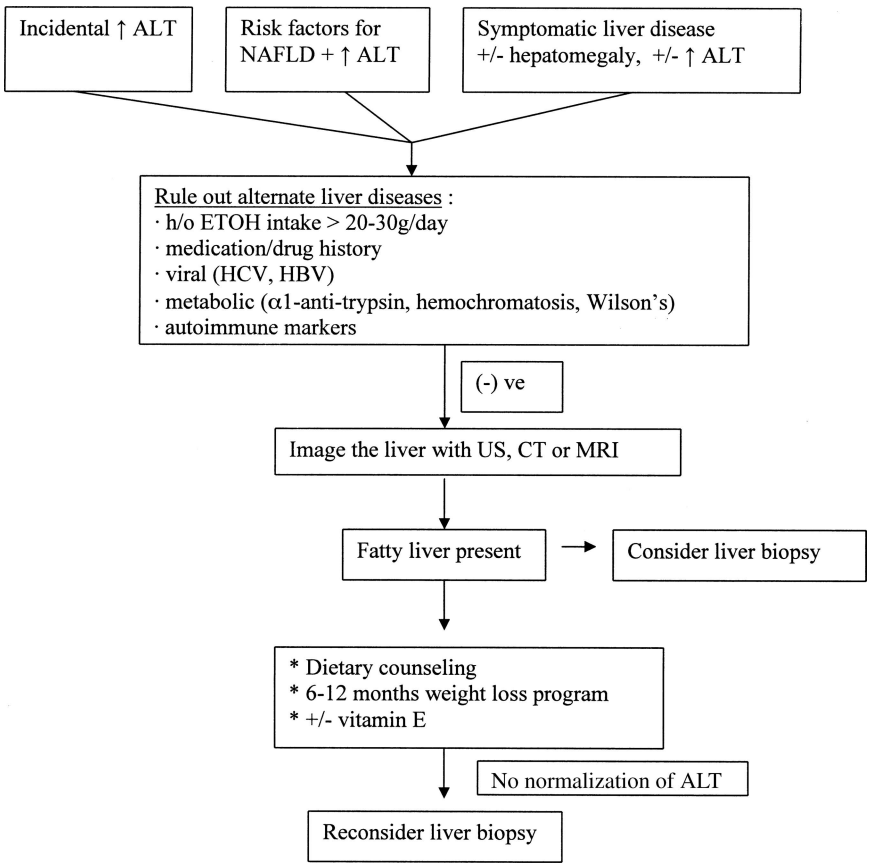

Fig 1. Diagnostic Approach to NAFLD.

In general, patient heterogeneity coupled with relatively short durations of follow-up has confounded interpretation of results from natural history studies. Cross-sectional studies of NAFLD indicate that most subjects have fatty liver alone (2) and it is widely believed to be rare for such patients to progress to steatohepatitis or fibrosis over time (5). Three studies, one with a follow-up exceeding 20 years (27), corroborate these viewpoints. Isolated reports of progression to steatohepatitis in the posttransplant setting (52) or in the morbidly obese following rapid weight loss surgery (12, 53) can be found in the literature. Advanced hepatic fibrosis is found in 30–40% of patients at the time of diagnosis (26, 33), whereas well-established cirrhosis is found in 10–15% of patients (2, 26, 27, 33). Studies have also suggested progression to hepatocellular carcinoma (54). The coexistence of steatosis with other liver diseases, such as HCV, could accelerate progression of the liver disease (55).

The importance of relating the natural history of NAFLD to the different histologic forms has been reported in a retrospective study (56). Although there was no significant difference in overall death rates among "simple steatosis," "steatohepatitis," and "fibrosis," liver-related death was increased in NAFLD patients with histologic necrosis. This study also confirmed the indolent clinical course and histologic sequelae of simple steatosis. A recently published clinicopathological natural history study followed 22 NAFLD patients by repeat biopsies after a mean of 5.7 years. Most had NASH on initial biopsy. A variable histological course was noted. One-third had fibrosis progression and one-third of these had rapid progression to advanced fibrosis, with the only clinical correlate of histologic progression being a higher serum AST (57).

Recent data suggest that NASH may be a major cause of "cryptogenic" cirrhosis and that many patients undergoing liver transplantation for so-called cryptogenic cirrhosis may, in fact, have "burned-out" NASH (58, 59). Caldwell *et al.* studied risk factors for liver disease in 70 patients with cryptogenic cirrhosis and found that diabetes and/or obesity were present in 74% of these patients and were significantly more common in these patients than in patients with cirrhosis secondary to primary biliary cirrhosis or HCV (58). None of those with cryptogenic

TABLE 2. GRADING AND STAGING OF HISTOPATHOLOGICAL LESIONS OF NONALCOHOLIC FATTY LIVER DISEASE

Grading for steatosis
Grade 1: <33% of hepatocytes affected.
Grade 2: 33 to 66% of hepatocytes affected
Grade 3: >66% of hepatocytes affected
Grading for steatohepatitis
Grade 1, mild
Steatosis: predominantly macrovesicular; involves up to 66% of lobules
Ballooning: occasionally observed; zone 3 hepatocytes
Lobular inflammation: scattered and mild acute inflammation (polymorphonuclear cells) and occasional chronic inflammation (mononuclear cells)
Portal inflammation: none or mild
Grade 2, moderate
Steatosis: any degree; usually mixed macrovesicular and microvesicular
Ballooning: obvious and present in zone 3
Lobular inflammation: polymorphonuclear cells may be noted in association with ballooned hepatocytes; pericellular fibrosis; mild chronic inflammation may be seen
Portal inflammation: mild to moderate
Grade 3, severe
Steatosis: typically involves >66% of lobules (panacinar); commonly mixed steatosis
Ballooning: predominantly zone 3; marked
Lobular inflammation: scattered acute and chronic inflammation; polymorphonuclear cells may be concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis
Portal inflammation: mild to moderate
Staging for fibrosis
Stage 1: zone 3 perivenular, perisinusoidal, or pericellular fibrosis; focal or extensive
Stage 2: as above, with focal or extensive periportal fibrosis
Stage 3: bridging fibrosis, focal or extensive
Stage 4: cirrhosis

Note. From Ref. 50.

cirrhosis had NASH on liver biopsy but 48% had mild to moderate macrosteatosis with necroinflammation. Loss of fatty infiltration has been documented in patients with NASH-associated cirrhosis, which may explain the relative paucity of steatosis in these patients with cryptogenic cirrhosis (27).

The precise risk of mortality in patients with NAFLD is not known and there is a critical need for prospective studies in this area. Many nonliver factors, e.g., obesity, diabetes, and their associated complications, contribute to mortality in patients with NAFLD. There are no published data concerning the relative contributions of these or the precise incidence of the liver-specific complications (variceal hemorrhage, ascites, and hepatocellular carcinoma) (30). All of the studies on the natural history of NAFLD/NASH have included highly selected patients from referral centers, and the generalizability of the results to the community at large remains uncertain. Final resolution of existing controversies and better definition of the natural history of NAFLD will require large, prospective, population-based, epidemiologic studies that track affected individuals for several decades.

TREATMENT

Management of Associated Conditions

No effective treatment has been demonstrated to alter the natural history of NAFLD. In the absence of therapeutic modalities of proven efficacy, therapy is directed toward correction of the risk factors for NASH.

Weight Management. An appropriate diet and exercise program is important. Several anecdotal studies have shown that moderate (~10%), sustained, and gradual weight loss may lead to an improvement in liver biochemistries and histology (60, 61). However, there are no randomized clinical trials of weight control as a treatment for NAFLD. Obese subjects may also benefit from weight loss because of its benefits on their cardiovascular risk profile (62). The optimal rate and degree of weight loss have not been established (63), and in patients with a high degree of fatty infiltration, very rapid weight loss may cause worsening of steatohepatitis and may precipitate liver failure (12). Also, the risk of gallstone disease increases exponentially when the rate of weight loss exceeds 1.5 kg/week (64). Pharmacologic and bariatric surgical strategies have also been described as aggressive modalities for controlling weight. It remains to be proven whether the risk-to-benefit ratio of appetite-suppressing medications justifies their use in NAFLD (63). The proximal gastric bypass operation has been shown to be superior to vertical-banded gastroplasty and jejunoileal bypass for morbidly obese subjects (BMI, >35 kg/m^2) (65, 66). However, there is still a risk of developing decompensated liver disease during rapid weight loss postoperatively (12).

Insulin Resistance. This appears to be the most reproducible predisposing factor for NAFLD. There are no controlled data on the use of pharmacologic agents for the management of NASH by controlling insulin resistnace. Thiazolidinediones are a class of drugs that stimulate peroxisome proliferator activated receptors (PPAR). An insulin-sensitizing medication, troglitazone (a thiazolidinedione), administered for 3–6 months in a small, nonrandomized series showed normalization of ALT in 7 of 10 subjects, and although necroinflammation was still noted on follow-up liver biopsy in all 7, the grade of inflammation had improved in 4 subjects (67). Troglitazone was later withdrawn from the U.S. market by the FDA after it was shown to induce an idiosyncratic hepatocellular injury. Even with the other thiazolidinediones, there is concern regarding the long-term safety of this group of drugs

in patients with liver disease. Data from animal models and several case reports have described hepatotoxic effects of resiglitazone and pioglitazone (68). In a recently published single-arm, open-label trial, 30 subjects with biopsy-proven NASH were administered rosiglitazone, 4 mg twice daily for 48 weeks (69). The drug was shown to improve insulin sensitivity and resulted in improved histologic markers of NASH, an observation suggesting that insulin resistance contributes to its development and that improving insulin sensitivity may be important in treating the liver disease, thus mandating a larger, placebo-controlled trial using rosiglitazone. A small pilot study with pioglitazone for 1 year in 18 NASH patients without diabetes also resulted in significant improvements in insulin sensitivity, serum ALT, and histologic features (70). Both rosiglitazone (69) and pioglitazone (70) led to an increase in BMI as well as peripheral distribution of fat, which would have obvious unpleasant cosmetic effects for patients. Metformin (a biguanide) is another antidiabetic medication improving hepatic insulin sensitivity. In a recent small study, when administered for 4 months, metformin was associated with an improvement in serum aminotransferases (71). These individuals also had a significant decrease in hepatic volume and body weight. It is uncertain if the improvement in liver disease was because of weight loss or due to metformin. Unfortunately, no posttreatment liver histology was obtained and the use of this drug remains experimental.

Lipid-Lowering Agents. Hypertriglyceridemia is often associated with NAFLD, hence the rationale for lipid-lowering agents in its management. In a pilot study, clofibrate (2 g/day) had no beneficial effect in liver tests or hepatic histology after 1 year of treatment (72). In another small controlled trial, gemfibrozil (600 mg/day for 4 weeks) showed a significant improvement in ALT levels versus placebo, however, no histologic data are available (73). There are no data on the use of 3-hydroxy-3-methylgutaryl–coenzyme A reductase inhibitors for the treatment of NAFLD.

Pharmacologic Therapy Offering Hepatocyte Protection. A handful of therapeutic agents thought to offer hepatocyte protection have been used in NAFLD patients. Ursodeoxycholic acid (UDCA), and the anti-oxidants, betaine and vitamin E, have peer-reviewed published data. Other drugs, e.g., lecithin, β-carotene, selenium, and *N*-acetylcysteine, lack randomized controlled data.

UDCA. This hydrophilic bile acid with hepatoprotective properties was first evaluated in a pilot study, where it was associated with both improved liver enzyme levels and a decrease in hepatic steatosis (72). Despite four open-label, small-scale pilot studies suggesting benefits of UDCA in NASH, this was not borne out in the only randomized, placebo-controlled trial, where UDCA at 13–15 mg/kg/day for 2 years, although safe and well tolerated, was not associated with an improvement in liver biochemistry or histology as compared to placebo (74).

Vitamin E (α-Tocopherol). The observation that vitamin E decreases oxidative stress provides a rationale for its use in patients with NASH. One uncontrolled trial in children with NASH showed that supplementation with vitamin E (400 to 1200 IU daily) was associated with a significant decline in serum aminotransferases (75). Unfortunately, a flaw of the study is that, once again, histology was not one of the clinically relevant end-point measures. In a recently published prospective, double-blind, randomized, placebo-controlled trial (of only 45 patients), 22 subjects received combination vitamins E and C (1000 IU and 1000 mg, respectively) for 6 months (76). There was a significant improvement in fibrosis scores in the NASH patients receiving vitamins compared to baseline but no improvement in necroinflammation or ALT. However, this histologic improvement was not significantly different from the improvement seen in the placebo group. Thus, the results of this placebo-controlled trial indicates that 6 months of treatment with a combination of vitamins E and C is not better than placebo for patients with NASH (77). The efficacy of pioglitazone plus vitamin E was compared to that of vitamin E alone in a pilot controlled trial involving 21 patients (78). After 6 months, significant histologic improvements were seen only in the combination group, while mean serum ALT decreased significantly in both groups.

Betaine. Betaine, a normal component of the metabolic cycle of methionine, is a precursor of *S*-adenosyl methionine, a hepatoprotective factor. A potential role in the treatment of NASH was suggested in a pilot study involving 10 adult patients, where, after 1 year, there was a significant improvement in both biochemistry and histology (79). Similarly, a 25% improvement was seen in hepatic steatosis over an 8-week period, in a larger randomized, double-blind, placebo-controlled trial (80). The results need confirmation in large, long-term, prospective trials (30).

Liver Transplantation

Patients with NAFLD who develop end-stage liver disease should be evaluated for liver transplantation. Despite this life-extending therapeutic alternative, NAFLD has been shown to recur in the liver allograft, with rapid progression from steatosis to steatohepatitis (81). These reports of recurrent NASH posttransplant suggest that liver transplantation, per se, does not cure the underlying metabolic derangements and is likely multifactorial,

including persistent hypertriglyceridemia, obesity, diabetes mellitus, and corticosteroid therapy. Clearly, attention to weight management and adequate treatment of hyperglycemia and hyperlipidemia are major goals of therapy both pre- and posttransplant.

SUMMARY

NAFLD is an increasingly important chronic liver disease with a wide spectrum of histopathology, ranging from bland steatosis to cirrhosis. Insulin resistance and oxidative stress play critical roles in pathogenesis (1). NAFLD is often asymptomatic and discovered incidentally on routine laboratory screening. It may occur in isolation or in association with other liver diseases, such as HCV. Liver biopsy remains the most sensitive and specific means of providing prognostic information (1). In the absence of established therapies, treatment is generally directed at optimizing body weight and controlling risk factors. Liver transplantation is a therapeutic option for decompensated liver disease but NAFLD has the potential to recur in the allograft. Large, long-term, biopsy-controlled prospective studies will provide much-needed information about the natural history, treatment, and prognosis of this poorly understood disorder.

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