Nonalcoholic Steatohepatitis

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Opinion statement

Nonalcoholic steatohepatitis (NASH) is an important medical condition and there is great public health concern related to its increasing incidence and potential implications for the development of end-stage liver disease. NASH represents a progression beyond simple lipid deposition in the liver parenchyma, requiring histologic evidence for hepatocyte injury such as ballooning degeneration, Mallory bodies, and/or pericellular fibrosis that can potentially lead to progressive liver injury and eventually cirrhosis. It is believed that several insults contribute to the evolution of hepatic injury such as insulin dysregulation, lipid deposition, oxidative free radicals, and lipid peroxidation. Initial treatment protocols for NASH focus on various aspects of injury in an attempt to control insulin imbalances, improve lipid regulation, reduce free radicals, and ameliorate the inflammatory process. No therapy is conclusively beneficial in all individuals, but preliminary data suggest several approaches that hold promise.

Introduction

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of clinicopathologic entities unified by characteristic lipid deposition throughout the liver parenchyma in individuals without a history of excessive alcohol intake [1,2••]. Nonalcoholic steatohepatitis (NASH) describes the presence of steatosis in association with hepatocyte injury (ballooning degeneration and Mallory bodies or both) and in some cases evidence of significant fibrosis [2••,3–5,6•,7–10,11•,12–14,15•]. The ultimate consequence of NASH may be cirrhosis or end-stage liver disease (ESLD), as NASH has been identified as the main cause of cryptogenic cirrhosis [16,17]. Liver biopsies from patients with NASH show characteristics similar to those of alcoholic steatohepatitis (ASH), manifesting steatosis, Mallory hyaline, ballooning degeneration, and/or sinusoidal fibrosis in zone three. Like its alcoholic counterpart ASH, NASH is thought to be progressive and may initially or eventually show evidence of necrosis, fibrosis, or cirrhosis [2••].

NATURAL HISTORY

Several studies demonstrate that individuals with NASH are more likely to progress to cirrhosis than those with steatosis alone or steatosis and nonspecific inflammation (without NASH) [4,5]. Despite the risk for progression to end-stage liver disease in NASH, the accuracy of noninvasive methods to detect this progression have not been fully established [6•,7,18]. However, there are some clinical variables that may help predict the likelihood of progression. It has also been demonstrated that early findings of Mallory's hyaline, ballooning degeneration, or fibrosis (*ie*, signs of necrosis) are predictive of cirrhosis and death [4,8,15•]. Furthermore, age over 45 years, type 2 diabetes mellitus, and transaminase elevation (with an aspartate aminotransferase (AST)/ alanine aminotranferease (ALT) over 1) seem to confer an increased risk for progression to fibrosis [7]. Another study combined both clinical and laboratory data in a graded scoring system (including age, body mass index, serum ALT, and triglyceride levels) to define the likelihood of fibrosis, but neither system has yet been validated [9]. Although iron does not appear to be consistently associated with hepatic fibrosis, patients with hepatitis C and NASH have seven times the likelihood of developing significant hepatic fibrosis [10,11•].

EPIDEMIOLOGY PREVALENCE

The prevalence of NAFLD can range from 10% to 39% in various populations around the globe, including the United States, Europe, Japan, South America, Australia,

and the Middle East [2••]. Expert opinion based on previous population and autopsy studies suggests that the prevalence of NAFLD in the United States is approximately 20% [2••,12]. Accordingly, NAFLD is believed to be the most common liver disease in the Western world and its prevalence is increasing, especially as the rate of obesity increases [1,2••,6•,12]. The prevalence of the subgroup of individuals with NASH is less clear but is estimated to be between 1 % and 5 % [2••,8,15•].

RISK FACTORS

Among the many risk factors described for the development of NAFLD and NASH, the most prominent are obesity, insulin resistance, and hyperlipidemia [1,2••]. Additional risk factors include female gender and conditions associated with the metabolic syndrome; furthermore, NASH becomes increasingly prevalent as age increases [7]. The reported predilection for NASH in females has been challenged by several studies [3,14], but patients have a threefold increased risk, obese patients have a sixfold increased risk, and individuals with morbid obesity are at the highest risk for the development of NASH [13,15•]. On the other hand, some patients who develop NASH have none of the common risk factors and are not overweight [2••,3,4].

CLINICAL PRESENTATION

A troubling aspect of both NAFLD and NASH is that they are often clinically silent [4]. Because this disease occurs in both men and women and among all ethnicities, it must be considered in all individuals with elevated liver enzymes [2••]. Patients may present with fatigue, malaise, or mild abdominal pain, and the physical exam my reveal hepatomegaly in a minority of patients [2••,3,16]. Mild elevations in the hepatic transaminases (up to two to three times the upper limits of normal) are the most common laboratory abnormalities, though many patients have normal enzymes [1,2••,3–5,6•,7–10,11•,15•]. Ultrasound and computed tomography (CT) scans can detect steatosis, but they are not able to discriminate steatosis alone from NASH [18]. Ultrasound defines increased echogenicity in NAFLD, but fibrosis can have a similar sonographic appearance [18]. One study suggested that a nonenhanced CT of the abdomen is the most accurate test for the diagnosis of steatosis, but additional studies have not confirmed these findings [18,19•]. Magnetic resonance imaging has also been used to define steatosis, and magnetic resonance spectroscopy (MRS) offers the potential to quantify hepatic lipids [19•]. Unfortunately, preliminary studies show that MRS overestimates the degree of hepatic steatosis, but the technology still holds promise for the future use [19•].

DIAGNOSIS

A definitive diagnosis of NASH requires a liver biopsy. In addition to making the diagnosis, liver biopsy can determine presence of fibrosis (stage of liver disease) and necrosis, and establishes a histologic baseline for future monitoring [2••]. As suggested previously, a diagnosis of NASH requires a hepatic specimen demonstrating diffuse parenchymal steatosis with at least ballooning degeneration of hepatocyte, as the presence of focal inflammation is not sufficient to define NASH [2••,20]. Several histologic findings are considered necessary for the diagnosis of NASH, including steatosis (generally macrovesicular), hepatocellular ballooning (predominately in zone 3), and mixed lobular inflammation [8,20,21]. Additional contributory findings are fibrosis in the perisinusoidal regions, zone 1 hepatocytes with glycogenated nuclei, zone 3 hepatocytes with Mallory's hyaline, Kuppfer cells containing acidophilic bodies, lipogranulomas in the lobules, and hepatocytes containing megamitochondria [8,20,21]. A grading system used to classify these histologic findings defines four types of steatosis: type 1 is steatosis alone; type 2 is steatosis plus inflammation; type 3 is steatosis with ballooning degeneration; and type 4 is steatosis with sinusoidal fibrosis and inflammatory infiltrates (predominately leukocytes) with or without Mallory hyaline [8,20,21]. When using this grading system, a diagnosis of NASH requires the findings of type 3 or type 4. Another grading system for hepatic fibrosis in NASH has also been developed [21].

Histologically, ASH and NASH are indistinguishable, so it is imperative to define the quantity of alcohol the patient typically consumes [22]. Epidemiologic studies report a range in alcohol intake associated with ASH, but recent data suggest that consumption greater than 20 g daily is considered excessive [23]. It is also important to remember the gender differences in predisposition to alcohol-related liver disease. To make the diagnosis of NASH, female patients should not have consistently consumed more than 20 g of alcohol daily and male patients no more than 30 g daily [1,2••]. However, lesser amounts of alcohol may accelerate the rates of progression in individuals with established steatosis or its risk factors such as obesity. Unfortunately, obtaining accurate alcohol intake history is often difficult, as patients usually underestimate their alcohol intake.

PATHOGENESIS

The pathogenesis of NASH is incompletely understood, but experts support the notion of a "multi-hit" process [24–29]. The initial hepatic insult, which may never progress further, is thought to be the development of macrovesicular steatosis, with accumulation of hepatic fat resulting from increased uptake and synthesis of fatty acids [1,2••]. The development of steatosis is likely to be related to dysregulation of fatty acids associated with elevated serum insulin levels from insulin resistance [25]. Steatosis may predispose the liver to oxidative stress, which is thought to be the second

hepatic insult. Oxidative stress, in turn, promotes lipid peroxidation in the membrane of hepatocytes thereby initiating the secretion of proinflammatory cytokines that activate stellate cells resulting in fibrosis [26]. Lipid peroxidation in the hepatocyte membrane from circulating free radicals can cause cell death and hepatic necrosis as well as producing toxic byproducts [26]. Elevated levels of fatty acids and insulin can catalyze lipid peroxisomes (either through CYP2E1 or CYP4A) and inhibit lipid oxidation in the mitochondria thus extending the process [27]. Mitochondria are likely to play an important role in the generation of reactive oxygen species and the acceleration of oxidative stress [28]. There may be concomitant upregulation of CYP2E1 or CYP4A that augments this cycle by increasing oxidative stress through increased lipid peroxidation, regulated by the peroxisome proliferator-activated receptor a (PPARa) [14,29]. Although peroxisomes play the largest role in oxidative stress, mitochondria, neutrophils, macrophages, and Kuppfer cells can also release free oxygen radicals [24,26,29]. Additionally, micronutrient malabsorption may reduce the intake of intrinsic antioxidants that might otherwise counterbalance this effect [30]. Furthermore, endotoxemia may promote hepatic inflammation by enhancing circulating cytokine, TNF-a [24,26].

Despite the potential role of each process, a combination of several processes probably induces excess oxidative stress, promoting inflammation and hepatocyte damage. These chronic hepatocyte insults induce stellate cells, promoting fibrogenesis [24,26]. It is important to remember that not all individuals with steatohepatitis develop fibrosis. One important variable in this process may be related to leptin that is produced by stellate cells [31–33]. Leptin interacts with inflammatory processes that may augment oxidative stress and promote fibrogenesis [31]. Obese individuals tend to have higher levels of leptin because of leptin resistance [32]. Perhaps serum leptin levels alter the balance in patients with steatosis, promoting steatohepatitis and the development of hepatic fibrosis [32,33].

Treatment

- Despite recent advances in our understanding of the pathophysiology of NASH, no single approach has convincingly been shown to prevent NASH or change its potentially progressive course. Many clinical trials have been conducted, but the quality of evidence is limited by insufficient numbers of enrolled patients, the use of intermediate outcomes, brief therapy duration, or suboptimal study design. In general, these treatment approaches have attempted to address imbalances in lipid regulation, excesses in oxidative stress, insulin homeostasis, or the inflammatory/fibrotic processes.
- Efforts to improve the metabolic syndrome with weight reduction produce some improvement in transaminases over short periods of time. Some studies using weight reduction have used intermediate markers to demonstrate decreased degrees of steatosis, but few studies have shown consistent improvement in fibrosis [34–36]. There is no clear advantage to any particular approach to weight loss. In fact, a recent systematic review showed no clear evidence that weight loss can improve any of the important outcomes of NAFLD [37••]. Rapid weight reduction may initially increase inflammation and should not be encouraged [38]. Dietary intake of amino acid supplements or the use of oral antibiotics after weight-reduction surgery may decrease the likelihood of developing steatosis over time, but the efficacy of these treatments has not been established [39].
- Nearly two dozen studies have evaluated various pharmacologic agents to treat patients with NAFLD or NASH. Unfortunately, most of the published literature represents openlabel uncontrolled studies and only a few randomized controlled clinical trials are reported [40–42,43••,44••,45–54,55••,62]. Several other studies have not been yet been published beyond abstracts reported at meetings. Some of these investigated treatment regimens and related data are summarized here.
- Systematic review of the literature showed no conclusive benefit to weight loss [37••].

Diet and lifestyle

- Caloric restriction to 25 cal/kg/d with exercise showed biochemical improvement.
- Modest weight loss improved biochemical or histologic abnormalities [46].

Surgical therapy

Gastric and intestinal bypass

Although the old surgical techniques were associated with adverse outcomes and increased risk for development of liver failure [47,48], more recent Bariatric surgical techniques are associated with biochemical and histologic improvement of patients with NAFLD.

Not currently recommended.

Biliopancreatic diversion

Some improvement in liver fibrosis in a case series [49].

Gastroplasty

Overall reduction in steatosis, but an increased percentage with lobular hepatitis is shown postoperatively [50].

Pharmacologic therapy

Insulin-modulating

Troglitazone

A thiazolidinedione and PPARg ligand that enhances insulin sensitivity [45,51]. Some biochemical and histologic improvement in patients with NASH. No longer available due to reports of liver dysfunction and liver failure.

Rosiglitazone

A thiazolidinedione and PPARg ligand that enhances insulin sensitivity [52]. Some improvement in liver enzymes and histology in open-label study of patients with NASH.

Standard dosage 4 mg once or twice daily.

Main side effects Weight gain, edema, headache, hyper-/hypoglycemia, diarrhea, anemia, congestive heart failure or pulmonary edema, increased transaminases or bilirubin, hepatitis, hepatic failure, pulmonary edema.

Cost effectiveness Two 2-mg tablets cost $3.82.

Pioglitazone

A thiazolidinedione and PPARg ligand that enhances insulin sensitivity [53,54,55••]. Some improvement in liver enzymes and histology in open-label study of patients with NASH.

Standard dosage 15 to 45 mg orally daily.

Main side effects Weight gain, edema, headaches, hypoglycemia, anemia, myalgias, decreased serum triglycerides levels,congestive heart failure, elevated creatine phosphokinase levels, increased transaminases, hepatic failure (rare), hepatitis.

Cost effectiveness Two 15-mg tablets cost $6.07 per day.

Metformin

	A biguanide that decreases hepatic glycolysis and intestinal absorption of glucose and increases insulin peripheral tissue glucose uptake and utilization [56]. Some improvement in liver enzymes and radiologic assessment of fat in an open-label pilot study of NAFLD.
Standard dosage	500 mg one to three times daily, unclear duration; maximum dose of 2550 mg daily short duration or 2000 mg daily for extended release.
Main side effects	Lactic acidos is rare, but possible; nausea/vomiting, diarrhea, abdominal pain, headaches, weakness; chest pain, flushing, palpitations, lightheadedness, rashes, alteration in bowel habits, heartburn, myalgias, dyspnea, flu-like syndrome, megaloblastic anemia.
Cost	Three 500-mg tablets cost $2.35.

Lipid-modulating therapy

Clofibrate

	A fibric acid that lowers lipids, probably by reducing cholesterol synthesis in the liver and transfer of triglycerides from the liver [57]. Conflicting data regarding biochemical improvement.
Standard dosage	500 mg orally four times daily.
Main side effects	Nausea, diarrhea, less commonly headaches, dizziness, nausea/vomiting, diarrhea, abdominal pain, muscle cramping/pain, weakness, arrhythmias, Stevens-Johnson syndrome, leukopenia, anemia, rhabdomyolysis, pancreatitis, elevated transaminases.
Special points	Not available in the United States.

Gemfibrozil

	A fibric acid with lipid-lowering activity [41]. In a clinical trial, some biochemical improvement in patients with NAFLD was reported.
Standard dosage	1200 mg/d orally in two divided doses, take 20 to 30 minutes before morning and evening meals.
Main side effects	Dyspepsia most common; less commonly: fatigue, vertigo, headache, eczema, rash, nausea/vomiting, abdominal pain or diarrhea, constipation; rare but important: anaphylaxis, angioedema, bone marrow hypoplasia, cholecystitis, depression, dermatomyositis, drug-induced lupus-like syndrome, exfoliative dermatitis, leukopenia, myasthenia, myopathy, pancreatitis, peripheral neuropathy, photosensitivity, Raynaud's, retinal edema, rhabdomyolysis, seizures, syncope, thrombocytopenia, vasculitis.
Cost effectiveness	Gemfibrozil: 1200 mg cost $0.57 a day. Lopid: (Pfizer, New York, NY) 1200 mg cost $3.07 per day.

Orlistat

	A reversible inhibitor of lipase that blocks fat digestions and induces steatorrhea [59]. In patients with NAFLD, possible improvement of liver enzymes and histology, most likely related to weight loss, were reported.
Standard dosage	120 mg three times daily taken with meals.
Main side effects	Headache, stearrohea, abdominal pain/discomfort, flatus/discharge, fecal urgency and incontinence, increased bowel movements, back pain, upper respiratory infections, menstrual irregularities, rectal pain, nausea and vomiting, arthritis/myalgias. Rare, but important are anaphylaxis, angioedema, pruritus, and rash.
Special points	Potential need for fat-soluble vitamin supplementation, not to be taken within 2 hours of taking Orlistat; substantial weight loss is possible; oxylate stones can develop.
Cost effectiveness	Three 120-mg tablets cost $3.57.

Betaine

	Metabolite of choline thought to decrease hepatic steatosis [60]. Possible biochemical improvement in NAFLD.
Standard dosage	3 to 20 g in divided doses.
Main side effects	Nausea, gastrointestinal distress, and diarrhea.
Cost	Unknown.

Probucol

	Decreases bile acid resorption and, therefore, cholesterol levels [44••]. Some biochemical improvement in NASH.
Standard dosage	500 mg orally twice daily taken with morning and evening meals.
Main side effects	(Minimal reported) QT prolongation, serious arrhythmias; dizziness, headache, peripheral numbness, diarrhea, abdominal pain, nausea/vomiting.
Special points	Not available in the United States.

Fibrosis-modulating or cytoprotection

Ursodeoxycholic acid

	A bile acid that may replace more hepatotoxic bile agents; may have cytoprotective effects [43••,53]. Randomized clinical trial did not show benefit of the relatively low dose of ursodeoxycholic acid (13 to 15 mg/kg/d).
Standard dosage	13 to 15 mg/kg/d in 4 divided doses with meals, unclear duration.
Main side effects	Headache, constipation, dizziness (approximately 15%), rashes, alopecia, diarrhea, leukopenia, allergy, abdominal pain, fatigue, nausea/vomiting, pruritis.
Cost	Actigall (Novartis Pharmaceuticals, East Hanover, NJ), three 300-mg tablets cost $11.48. Urso, three 250-mg tablets cost $6.10.

Oxidative stress-modulating

Vitamin E (a-tocopherol)

	Fat-soluble vitamin with presumed antioxidant effects [61]. In open-label pilot study, some biochemical improvement in children.
Standard dosage	Recommended daily allowance is 15 mg; daily intake should not exceed 1000 mg/d.
Main side effects	Blurred vision, gonadal dysfunction.
Cost	Three 400-IU tablets (approximately 1000 mg) cost $0.18.

Vitamin E & Vitamin C (a-tocopherol and ascorbic acid)

	Vitamin C is a water-soluble vitamin with presumed antioxidant effects [40].
Standard dosage	Recommended daily allowance should not exceed 2000 mg/d.
Main side effects	Hyperoxaluria, dizziness/faintness/fatigue, flank pain, headache.
Cost effectiveness	Three 400-IU tablets of vitamin E (approximately 1000 mg) cost $0.18. Two 500-mg tablets of vitamin C is $0.04. Total of $0.22.

N-Acetylcysteine

	A prodrug of glutathione that can help modulate production of reactive oxygen species in the liver [62]. Some biochemical improvement.
Standard dosage	1 g daily, unclear duration.
Main side effects	(Most reported from intravenous administration or inhalation.) Drowsiness, fevers/chills, nausea/vomiting, stomatitis.
Cost	Two 600-mg tablets cost $0.48.

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