Diagnosis and Therapy of Nonalcoholic Steatohepatitis

The increasing prevalence of obesity, insulin resistance, and the metabolic syndrome has significant implications for the future of chronic liver disease. The resultant increase in the number of patients with nonalcoholic fatty liver disease (NAFLD) is expected to translate into increased numbers of patients with end-stage liver disease (cirrhosis), liver failure, and hepatocellular carcinoma. It is particularly important to identify the patients who are at greatest risk of these aforementioned complications of chronic liver disease, those nonalcoholic fatty liver disease patients with nonalcoholic steatohepatitis. Currently liver biopsy is the gold standard for diagnosis, but less invasive, highly accurate, and affordable screening tools are required. These tools may include radiologic or laboratory studies to identify patients noninvasively who may benefit from therapeutic interventions. Clinical scoring systems that may be used in general practice as initial screening tools also may prove useful. Most therapeutic modalities available or under development target the major pathways thought essential in the pathogenesis of nonalcoholic steatohepatitis and often are directed at reducing body mass index and improving insulin resistance via pharmacologic, surgical, dietary, or exercise regimens. Other potential therapeutic agents directed at cytoprotection or reduction of fibrosis are under investigation. This article focuses on diagnosis and therapy available and under development for this chronic liver disease.

Because obesity has become commonplace in today's modern society, the face of chronic liver disease is changing to reflect a significant increase in patients with features of the metabolic syndrome, leading to an increased prevalence of nonalcoholic fatty liver disease (NAFLD). It is estimated that 30% of the adult population in the United States now has NAFLD, with an increasing prevalence to 90% in morbidly obese populations presenting for bariatric surgery.1–3 This is worrisome because patients with NAFLD appear to have a higher all-cause mortality in addition to liver-related cause of death and recent data points to an increased risk for cardiovascular disease.4–8 However, in clinical and histopathologic studies, the course of isolated fatty liver appears more indolent and less likely to progress to advanced liver disease.9 Alternatively, a subset of NAFLD patients have a more aggressive form of fatty liver known as nonalcoholic steatohepatitis (NASH), in which patients are at greater risk for progression to cirrhosis, end-stage liver disease, and likely hepatocellular carcinoma. It is estimated that 3%–6% of the United States population has NASH, with upwards of 30% of morbidly obese patients showing features of NASH.3,10

Because of the inordinately high prevalence of NAFLD, it is important to identify those patients with NASH, particularly those at risk for advanced disease. Liver biopsy traditionally has been the gold standard used to make the diagnosis of NASH. However, without adequate biopsy tissue, there is a high degree of sampling variability. Additional problems include the small but inherent risk of complications, potential patient discomfort, and cost. Subsequently, noninvasive tools to correctly identify NAFLD patients who have histopathologic evidence of NASH with or without advanced fibrosis are in development and include a variety of techniques that vary from composite laboratory and biomarker data to tests that
measure hepatic tissue elasticity such as the Fibroscan (Echosens, Paris, France).

Establishing the diagnosis of NASH is helpful only if an appropriate care plan can be developed and this includes providing an effective treatment for the disease. These therapeutic modalities should be readily available, safe, effective, and relatively inexpensive. Therapies that target the underlying metabolic syndrome through lifestyle modification, dietary adjustments, exercise regimens, bariatric surgery, or medications are all potential avenues of treatment. Other potential therapeutic targets include cytoprotective and antifibrotic agents. This article focuses on the diagnostic and therapeutic tools currently available as well as those under investigation for future clinical use.

**Diagnosis**

Patients with NAFLD often are asymptomatic and come to attention secondary to mild to moderate increases in hepatic aminotransferase levels or abnormal liver appearance on abdominal imaging. Liver enzyme level increases tend to show an alanine aminotransferase (ALT) predominance and rarely are increased more than 3 times the upper limits of normal. The alkaline phosphatase level occasionally may be increased mildly, and rarely is the only liver enzyme abnormality identified.

Conventional radiology studies used in the diagnosis of fatty liver include ultrasound (US), computed tomography (CT), and magnetic resonance (MR) imaging (Table 1). US can identify hepatic steatosis with reasonable accuracy. Typical criteria used to assess for steatosis include hepatorenal echo contrast, liver brightness, deep (posterior beam) attenuation, and vascular blurring. A recent Italian study of 235 patients showed an excellent specificity of 97%, but a lower sensitivity of 64%. This increased to 100% specificity and 89.7% sensitivity when only including patients with at least 30% steatosis. Hamaguchi et al. used a 6-point scoring system based on liver brightness, attenuation, and vascular blurring on US to evaluate for NAFLD and showed 100% specificity and 91.7% sensitivity when compared with liver biopsy. However, this study was performed in relatively thin patients. When performed in morbidly obese patients, others have shown the sensitivity and specificity to be only 49.1% and 75%, respectively, for identifying steatosis.

Other studies have emphasized the difficulty in distinguishing steatosis from fibrosis on US and the inability of US to correlate with the other essential hepatic histology required for the diagnosis of NASH. CT has shown a similar diagnostic yield similar to US. Unenhanced CT is accurate in predicting steatosis of greater than 30%, but has been shown to be much less accurate in predicting lower-grade steatosis. Diagnostic accuracy has been improved with unenhanced CT scan using liver:spleen attenuation ratios with up to 100% specificity and 82% sensitivity for hepatic steatosis greater than 30%.

Hepatic steatosis may be quantified from MR imaging based on the signal differences between fat and water and shows good correlation with microscopic fat content. Limitations of this modality include expense, inability to use in patients with implantable devices or claustrophobia, and altered values in patients with iron overload. Magnetic resonance spectroscopy is a specialized radiologic study that can measure triglyceride content noninvasively. This technique was used on 2349 patients from the Dallas Heart Study with highly reproducible and accurate results, but widespread application of this technology is limited by cost and availability.

As a group, radiologic studies have been shown to identify hepatic steatosis accurately and often bring a group of asymptomatic patients to clinical attention. Occasionally, patients with NAFLD are symptomatic and describe a fullness or discomfort in their right upper quadrant that does not appear to be associated with severity of disease. Physical examination generally is normal with the exception of the common finding of hepatomegaly. A novel finding of increased dorsocervical lipohypertrophy in patients with NAFLD was described recently by Cheung et al. Interestingly, dorsocervical lipohypertrophy was found to be the single greatest contributor to the severity of histologic findings of steato-

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**Table 1. Radiology Studies in the Diagnosis of NAFLD**

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>49%–89%</td>
<td>75%–100%</td>
<td>Identifies steatosis only</td>
</tr>
<tr>
<td>Levovist US</td>
<td>100%</td>
<td>100%</td>
<td>Small preliminary study of 64 patients—potentially useful in NASH patients</td>
</tr>
<tr>
<td>CT with liver-spleen attenuation ratios</td>
<td>54%–93%</td>
<td>95%</td>
<td>&gt;30% steatosis, cannot differentiate NASH</td>
</tr>
<tr>
<td>MR imaging2</td>
<td>NA</td>
<td>NA</td>
<td>Highly accurate in determining steatosis &gt;30%</td>
</tr>
<tr>
<td>MR spectroscopy2</td>
<td>NA</td>
<td>NA</td>
<td>Highly accurate for steatosis</td>
</tr>
<tr>
<td>MR elastography3</td>
<td>87%</td>
<td>91%</td>
<td>Good for both steatosis and fibrosis; early studies only</td>
</tr>
<tr>
<td>US elastography6</td>
<td></td>
<td></td>
<td>For stage 4 fibrosis, cannot differentiate NASH (accuracy in obese patients is unknown)</td>
</tr>
</tbody>
</table>

Radiology Studies in the Diagnosis of NAFLD
hepatitis and may prove to be a useful tool in the diagnosis of NASH.

NAFLD patients typically meet criteria for the metabolic syndrome as defined by the American Heart Association and National Heart, Lung, and Blood Institute, with prevalence rates reported from 47% to 71%. In addition, the presence of the metabolic syndrome has been linked to NASH as well as severe fibrosis in NAFLD patients on multivariate analysis. Defining criteria for the metabolic syndrome (applying the earlier-described society guidelines) include any 3 of the following 5 laboratory and physical examination findings: increased waist circumference (men, >40 in; women, >35 in), increased triglyceride levels of 150 or higher, reduced high-density lipoprotein (HDL) levels of less than 40 mg/dL in men or less than 50 mg/dL in women, increased blood pressure of greater than 130 mm Hg systolic or greater than 85 mm Hg diastolic, or increased fasting glucose level of greater than 100 mg/dL systolic or greater than 85 mm Hg diastolic, or increased triglycerides of greater than 150 mg/dL. Lipid and glucose measurements are considered positive if the patient is already on cholesterol- or glucose-lowering medications.

Percutaneous liver biopsy remains the standard for distinguishing isolated fatty liver from NASH. Key histopathologic criteria seen with NASH include macrovesicular steatosis, lobular inflammation, hepatocyte ballooning, and often perisinusoidal/perivenular fibrosis as well as Mallory–Denk bodies. However, agreement among pathologists is not universal. The NAFLD activity score (NAS) is a histologic scoring system that was developed by the National Institutes of Health–sponsored NASH Clinical Research Network, which focuses on steatosis, lobular inflammation, and hepatocyte ballooning. A NAS of 5 or greater is consistent with NASH and a score of 2 or less is not associated with NASH, with scores of 3 or 4 falling somewhere in between. The NAS was not intended to be used as a diagnostic tool, but rather to provide a uniform tool for assessing disease severity, ideally in clinical trials.

Recent data have shown that significant sampling variability exists for fibrosis and inflammation, although this may be attenuated with good core biopsy samples. Unfortunately, adequate biopsy samples remain an issue and given the significant prevalence of NAFLD coupled with the previously described limitations of biopsy, fewer invasive tests are being developed to identify NASH with or without advanced fibrosis. These diagnostic modalities can be divided into tests using image analysis and tests that combine biomarker and clinical data.

**Imaging for NASH**

An important limitation of all imaging modalities including CT scan, US, and MR imaging is the inability of these techniques to differentiate isolated hepatic steatosis from steatohepatitis. The definitive study by Saadeh et al of 90 consecutive patients with biopsy-proven NAFLD who underwent CT, US, and MR imaging clearly showed that these radiologic studies were unable to accurately discriminate between NASH and isolated fatty liver. All 3 radiologic studies were best able to predict 33% or greater steatosis, but were not accurate in assessing for any features of steatohepatitis.

Novel techniques are under development that may prove to be useful radiologic tools to diagnose NASH noninvasively. One such idea involves contrast ultrasound using Levovist (Shering, Berlin, Germany), with delayed images taken at 5- to 10-minute increments for 50 minutes, and has shown great accuracy in diagnosing NASH with a receiver operating curve (ROC) of 100% among the 21 NASH, 33 NAFLD, and 10 healthy patient controls. This minimally invasive novel application of US requires further study but shows early promise as a diagnostic tool.

**Imaging for NASH Fibrosis**

Although efforts to use noninvasive imaging studies to accurately grade NAFLD in terms of NASH have been unsuccessful, the investigations that use imaging to stage fibrosis in patients, and thus identify those with advanced disease, have shown more promise. Transient elastography is an ultrasound-based technology that is used to measure liver stiffness. In a recent study of 68 patients with NAFLD, a stepwise increase in elasticity was shown with severity of hepatic fibrosis. This study showed good correlation between liver biopsy fibrosis stages 1–4 and liver stiffness using ROCs with positive predictive values (PPVs) between 64% and 93.5% for the varying stages of fibrosis. A recent meta-analysis of 9 studies using this technology showed pooled estimates for sensitivity and specificity of 87% and 91%, respectively, for patients with stage IV fibrosis and 70% sensitivity and 84% specificity for stages II–IV fibrosis. One important caveat that requires further investigation is that steatosis and high body mass index (BMI; >25) has been shown to reduce the reproducibility of this new technology.

An MR equivalent to transient elastography also has been investigated as a noninvasive means to evaluate for hepatic fibrosis. A recent study by Yin et al showed promising results yielding 98% and 99% sensitivity and specificity, respectively, for identifying the presence of any fibrosis. Hepatic steatosis also was identified correctly and the degree of steatosis did not seem to confound fibrosis measurements. One limitation of this initial study was that the liver biopsies were on average 6.5 months apart from the imaging study, but the significance of this separation is uncertain. Further study into this novel imaging technique is warranted. Both of these elastography techniques require large multicenter trials in conjunction with liver biopsy before they can be applied to regular clinical practice.
Table 2. Noninvasive Biomarkers in NASH

<table>
<thead>
<tr>
<th>Serum biomarker</th>
<th>Marker of</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROS</td>
<td>Oxidative stress</td>
<td>Conflicting results: some correlation between NASH and increased level of ROS</td>
</tr>
<tr>
<td>Leptin</td>
<td>Insulin resistance</td>
<td>Conflicting results: higher levels in some studies</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Insulin sensitivity</td>
<td>ADP lower in NASH patients</td>
</tr>
<tr>
<td>High-sensitivity CRP</td>
<td>Systemic inflammation</td>
<td>Conflicting results: some increased high-sensitivity CRP with NASH compared with NAFLD</td>
</tr>
<tr>
<td>Cytokeratin 18</td>
<td>Hepatic apoptosis</td>
<td>Significantly higher in NASH</td>
</tr>
</tbody>
</table>

**Differentiating Isolated Fatty Liver From NASH**

**Biomarkers**

Serum biomarkers that could be used as noninvasive tests to distinguish NASH from isolated fatty liver also have been investigated. One or several laboratory tests that could accurately identify, grade, and stage NASH would allow for screening of the large population of patients with NAFLD and avoid invasive and expensive liver biopsies. Several classes of biomarkers are in the initial stages of study that are directed at the pathways believed to be involved in the pathogenesis of NASH (Table 2).

Oxidative stress is presumed to be central to the pathogenesis of NASH and therefore biomarkers that measure oxidative stress through reactive oxygen species (ROS) have been looked at as potential surrogate markers of NASH. Chalasani et al compared serum levels of oxidized low-density lipoprotein (LDL) and thiobarbituric acid-reacting substances in 21 NASH patients with 19 control patients without liver disease of similar age, BMI, and nutritional intake. Significantly higher levels of lipid peroxidation products were seen in NASH patients, but limitations included a lack of liver biopsy in the control patients and small numbers overall. In contrast, no correlation between oxidative stress and steatosis or fibrosis was seen in another study of 64 patients with either NAFLD or viral hepatitis. These discordant results may reflect that hepatic oxidative stress is not reflected accurately by serum measurements, but further study is required to render a final verdict on the utility of measuring serum ROS in NAFLD/NASH patients.

Another area of interest has been serum measurements of specific adipocytokines (produced by adipose tissue) such as leptin and adiponectin (ADP). Obesity and excess caloric intake enhance up-regulation of leptin resulting in increased free fatty acid delivery to the liver, contributing to hepatic steatosis. Initial investigations showed an association between higher leptin levels and the presence of NASH as well as steatosis grade, although not inflammation or fibrosis. However, several subsequent studies have failed to show any associations between leptin levels and the presence or absence of hepatic steatosis, inflammation, or fibrosis.

In contrast to leptin, ADP is thought to promote insulin sensitivity and increase glucose utilization and free fatty acid oxidation in the liver. Hui et al found significantly lower serum levels of ADP in patients with NASH when compared with both normal controls and individuals with simple steatosis. Numerous other studies have confirmed that ADP is generally lower in NAFLD patients compared with healthy controls. Targher et al recently showed that ADP levels were associated closely with severity of liver histology to include hepatic steatosis, necroinflammation, and fibrosis. Although all 3 components of hepatic histology were associated with low ADP levels, only steatosis and necroinflammation were found to be independent predictors in multivariate analysis. Further study is required to fully delineate the relationship between ADP and severity of liver disease in NAFLD patients.

Other markers of systemic inflammation such as C-reactive protein (CRP) also have been studied with conflicting results. An Australian study found no difference between high-sensitivity CRP levels in patients with simple steatosis and NASH. This is in contrast to other studies showing significant increases in high-sensitivity CRP levels in patients with NASH compared with NAFLD controls. Given these conflicting results, CRP as a marker for hepatic inflammation requires further investigation, although its association with other disease processes may limit its clinical usefulness.

Hepatic apoptosis is a prominent feature of NASH, and, as such, biomarkers of hepatic apoptosis have been explored as a potential diagnostic tool. Wieckowska et al showed a striking relationship between plasma levels of caspase-generated cytokeratin-18, a protein involved in one of the final steps of apoptosis, and the histologic presence of NASH on liver biopsy. Similarly, Yilmaz et al measured serum levels of extracellular cytokeratin 18 (M30 antigen and M65 antigen) in patients with NAFLD and varying degrees of severity of NASH. Both of these antigens were found to be significantly higher in NASH patients with a sensitivity of 60–69% and a specificity of 87%–97% in predicting NASH if the antigen levels were markedly abnormal. The utility of cytokeratin 18 recently was validated independently in a study of 21 pediatric NAFLD patients, which directly correlated the level of cytokeratin-18 to severity of liver disease. This modality appears to offer significant promise as a future diagnostic tool to differentiate isolated fatty liver from NASH.
Scoring Systems for Identifying NASH From NAFLD

Scoring systems using one or several clinical and/or laboratory parameters to identify patients with NASH from the larger pool of NAFLD patients also have been assessed. Several studies have looked at a variety of variables that might prove suitable (Table 3). Palekar et al.62 developed a clinical model that sums 5 risks factors for NASH identified on multivariate logistic regression. These factors include age 50 or older, female sex, aspartate aminotransferase (AST) level of 45 or greater, BMI of 30 or greater, AST/ALT ratio of 0.80 or greater, and hyaluronic acid level of 55 or greater. Combining 3 or more of these factors yielded a sensitivity of 73.7% and a specificity of 65.7% for detecting NASH with an ROC of 0.763. This study provided a relatively simple means of identifying NASH patients but requires further validation in a larger study population.

A larger European study assessed the utility of the NASH Test (Biopredictive) to distinguish NASH from isolated fatty liver.63 This complex test including 13 clinical and laboratory parameters was developed using 160 patients in the training group, 97 patients in a multicenter validation group, and 383 control patients. Overall specificity was shown to be 94%, with a much lower sensitivity of 33% and an ROC of 0.763. This study provided a relatively simple means of identifying NASH patients but requires further validation in a larger study population. A larger European study assessed the utility of the NASH Test (Biopredictive) to distinguish NASH from isolated fatty liver.63 This complex test including 13 clinical and laboratory parameters was developed using 160 patients in the training group, 97 patients in a multicenter validation group, and 383 control patients. Overall specificity was shown to be 94%, with a much lower sensitivity of 33% and an ROC of 0.763. This study provided a relatively simple means of identifying NASH patients but requires further validation in a larger study population.

Distinguishing Advanced Fibrosis in NASH

The ability of one or several screening tests to predict hepatic fibrosis in patients with NAFLD also has been an area of intense interest. Study of potential surrogate markers of fibrosis have shown success in identifying those with advanced fibrosis but have been less accurate in predicting mild to moderate fibrosis (Table 3).64 One of the early scoring systems developed called the body mass index; age at liver biopsy; alanine aminotransferase; and serum triglycerides (BAAT) score used 4 easily determined clinical variables to assess for hepatic fibrosis.65 This scoring system showed good PPV in determining advanced fibrosis but fell short of an ideal screening test to identify mild to moderate disease. The same group expanded their efforts with the development of the FibroTest-FibroSURE (Biopredictive) based on H2macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, and \( \gamma \)-glutamyltransferase levels.66 A 90% negative predictive value (NPV) for advanced fibrosis and a 70% PPV for advanced fibrosis were noted in final analysis. The diagnosis of borderline NASH was harder to make with a 72% NPV and 74% PPV. This is an important limitation of the FibroTest-FibroSURE, which translates into one third of total patients enrolled still requiring a liver biopsy.

The European Liver Fibrosis study evaluated 1021 patients using 9 surrogate markers of fibrosis and developed an algorithm using 4 of these markers that showed 90% sensitivity in detecting fibrosis as well as 92% NPV in ruling out fibrosis.67 This study was limited in the fact that it combined patients with all types of chronic liver disease and requires further study in NAFLD-specific patient populations.

The NAFLD fibrosis scoring system, developed in collaboration between multiple liver centers, uses 6 commonly measured parameters including age, hyperglycemia, BMI, platelet count, albumin level, and AST/ALT ratio.68 This scoring system uses a 2-point cut-off system similar to the FibroTest-FibroSURE. By using a low cut-off score (−1.455), the NPV for excluding advanced fibrosis was 93% in the estimation group and 88% in the validation group. When a high cut-off score

### Table 3. Macronutrients in NAFLD

<table>
<thead>
<tr>
<th>Macronutrient</th>
<th>Found In</th>
<th>Action</th>
<th>Findings in NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fatty acids</td>
<td>Lard, butter, coconut oil, palm oil</td>
<td>Increases LDL</td>
<td>Higher intake in NASH patients</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>Olive oil, nuts, avocados, peanut butter, peanut oil</td>
<td>Higher intake decreases LDL, increases HDL</td>
<td>Uncertain</td>
</tr>
<tr>
<td>PUFAs (n-6)</td>
<td>Sunflower, corn oil</td>
<td>Decreases HDL, ↑ increase oxidative stress</td>
<td>High n-6/n-3 ratio in NASH patients</td>
</tr>
<tr>
<td>PUFAs (n-3)</td>
<td>Fish oil, walnuts, salmon, shellfish</td>
<td>Decreases FFA, glucose, insulin, TNF-( \alpha )</td>
<td>Higher intake decreases hepatic steatosis (small studies)</td>
</tr>
<tr>
<td>Trans fatty acids</td>
<td>Fast foods, baked goods, deep fried foods</td>
<td>Increases inflammatory markers and LDL</td>
<td>Uncertain</td>
</tr>
<tr>
<td></td>
<td>Dairy products (−5%)</td>
<td>(Naturally derived trans FAs do not have above actions)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ruminants (cows/sheep)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Margarine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucrose/fructose</td>
<td>Sweetened drinks/sodas, candy</td>
<td>Worsens insulin resistance</td>
<td>Higher intake in NASH patients</td>
</tr>
<tr>
<td>Protein</td>
<td>Meat, fish, eggs, dairy</td>
<td>Uncertain</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Fiber</td>
<td>Whole grains, fruits, and vegetables</td>
<td>Improve insulin resistance</td>
<td>Lower intake in NASH</td>
</tr>
</tbody>
</table>

TNF, tumor necrosis factor; ↑, conflicting data.
(0.676) was used, the PPV for predicting advanced fibrosis was 90% and 82%, respectively. Overall, the NAFLD fibrosis score predicted advanced fibrosis with an ROC of 0.82. The authors suggest that liver biopsies could therefore be avoided in 75% of patients. A separate validation study of 79 patients found the NPV for excluding advanced fibrosis to be 93%, but the PPV for predicting advanced fibrosis was only 42%. This lower PPV translates into fewer patients avoiding liver biopsy. Therefore, further validation is necessary before this or any other scoring system can be recommended broadly.

A recent review by Guha et al tabulated 29 studies that looked at noninvasive markers of hepatic fibrosis in NAFLD either as primary or secondary end points. This comprehensive review identified the key variables found in the majority of these studies, which included the presence of diabetes, increasing age, increased homoeostatic insulin resistance, increased AST/ALT ratio, decreased platelets, hyaluronic acid, and BMI. Although these models are good in predicting advanced fibrosis at any one time point, they fall short in defining an excellent screening test to identify patients with NASH noninvasively who are at risk of progressing to severe fibrosis.

**Treatment for NASH**

**Calorie Reduction**

Patients with NAFLD typically are overweight or obese, insulin resistant, and have a consistently higher energy intake when compared with individuals without hepatic steatosis. Data have shown that in the setting of obesity, moderate weight loss of approximately 6% via caloric restriction improves insulin resistance and intrahepatic lipid content. Furthermore, caloric restriction
improves serum aminotransferase levels and hepatic histology.73–77

The degree of caloric restriction has been questioned. A small study by Anderson et al74 showed that extreme weight loss via starvation leads to worsening liver histology, including fibrosis. In addition, 2 bariatric surgery studies have shown mild worsening of lobular inflammation and fibrosis in a subset of patients with a mean weight loss of 32 and 38 kg, respectively.78,79 In contrast, others have shown significant histologic improvement with weight loss through either caloric reduction or bariatric surgery.80–84 Huang et al85 counseled patients to follow a 1400 kcal/day diet for 12 months in 15 biopsy-proven NASH patients with a subsequent mean weight loss of 2.9 kg (3% of body weight). Among the 9 of 15 patients (60%) who had a histopathologic improvement on repeat liver biopsy, the average weight loss was 7%. Hepatic fibrosis did not change significantly in this small study. No significant change in fibrosis was also seen in a meta-analysis of 15 studies that evaluated weight reduction without bariatric surgery in the treatment of NAFLD. This intriguing article suggested that diets that improve insulin sensitivity, promote foods with low glycemic indices, and yield sustainable weight loss offer the most potential benefit, although well-designed clinical trials are lacking.

Another concept in the arena of dietary composition modification is the difference in the various types of dietary fat (Table 4). Excess SFAs have been shown to promote endoplasmic reticulum stress, hepatic steatosis, and inflammation in animal models, although it remains uncertain if a minimum intake of SFAs are required for optimal metabolism.87,93–95 On the other hand, monounsaturated fatty acids such as found in olive oil, peanut butter, nuts, and avocados are thought to be generally beneficial because they decrease total cholesterol, triglycerides, serum LDL, and maintain HDL. A small study of 11 insulin-resistant patients showed improvement in insulin resistance and increased adiponectin levels after 1 month of a monounsaturated fatty acid–enriched diet.86

Altering the amount of PUFAs in diets also has been studied. When PUFAs have been used to replace SFAs in the diet, significant cardiovascular benefits have been noted.97 Hepatic steatosis in obese mice also has been improved with dietary PUFAs via negative regulation of hepatic lipogenesis.98 The ratio of n-6 to n-3 PUFAs also seems to be important in predicting insulin resistance. An excessive amount of n-6 PUFAs with a high n-6/n-3 ratio was shown in a recent study of 45 NASH patients compared with 856 age- and sex-matched controls.99 N-3 PUFAs such as alpha-linoleic acid (fish oil) appeared to be beneficial in 2 small studies in patients with NAFLD with improvement in serum triacylglycerol concentrations, fasting glucose, liver enzyme levels, and hepatic steatosis.100,101 Walnuts are another source of alpha-linoleic acid that has been shown to improve lipid profiles in diabetes.102

On the other hand, trans fatty acids occurring in dairy foods as well as hydrogenated margarine products have been less well studied in patients with NAFLD. However, information in healthy subjects suggests that intake of these hydrogenated oils increases inflammatory markers and increases the LDL:HDL ratio.103,104 Based on these studies, general recommendations to avoid or reduce the intake of trans fatty acids seems reasonable. The increased intake of sucrose and fructose in Western diets also may play a role in the development of NAFLD. A recent population-based study showed that NAFLD patients consumed almost twice the amount of soft drinks than control counterparts.105 It has been speculated that the high fructose content of nondiet sodas is associated with increased hepatic de novo lipogenesis, hypertriglyceridemia, and hepatic insulin resis-
This corresponds to a recent study in a mouse model showing that rapidly absorbed carbohydrates promotes hepatic steatosis when compared with consumption of slowly absorbed carbohydrates with a lower glycemic index.107 This field of diet composition manipulation represents a new and intriguing area of study in the treatment of NASH that requires further study. Large RCTs are needed before final recommendations can be made as to the ideal diet for NAFLD patients. The general concept that foods with low glycemic index as well as diets containing more monounsaturated fatty acids and n-3 PUFAs, low SFAs, and limited to no fructose seem to be acceptable general guidelines to offer patients who are agreeable to lifestyle changes in their treatment.

**Exercise**

Exercise is another area of interest in the field of lifestyle modification as therapy for NAFLD although there are only limited data available. Most of the evidence that does exist uses exercise in combination with diet to promote weight loss. The general consensus has been that exercise works synergistically with diet modification to produce beneficial metabolic effects.108 Suzuki et al109 found that in a population of 348 male patients who received annual health physicals, regular exercise and weight loss over a 1-year period was associated with a significant improvement in serum aminotransferase levels. Another study that followed up 25 obese NAFLD patients prospectively for 3 months confirmed that regular exercise defined as walking or jogging daily along with a reduced-calorie diet produced significant improvement in serum aminotransferase levels, fasting glucose, and hepatic steatosis compared with a control population.110

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Biochemical effects</th>
<th>Histologic effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Weight loss</td>
<td>↓ LFTs and insulin resistance</td>
<td>↓ Steatosis, inflammation, NAS score</td>
<td>Improvement in inflammation and NAS seen if weight loss ≥ 9%</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>Weight loss, possible peripheral effects</td>
<td>↓ Insulin resistance, triglyceride levels, LFTs, HDL, adiponectin</td>
<td>↓ Steatosis</td>
<td>Animal data, psychiatric side effects</td>
</tr>
<tr>
<td>Incretin analogs</td>
<td>Weight loss</td>
<td>↓ LFTs, insulin resistance, hemoglobin A1C</td>
<td>↓ Steatosis</td>
<td>Animal and pilot studies in NAFLD; extensively studied in type 2 diabetes mellitus</td>
</tr>
<tr>
<td>TZDs</td>
<td>PPAR-γ agonists</td>
<td>↓ LFTs, insulin resistance, and TNF-α, Adiponectin</td>
<td>↓ Steatosis, inflammation and fibrosis</td>
<td>Side effects: weight gain, peripheral edema, cardiac, fractures, need for maintenance therapy</td>
</tr>
<tr>
<td>Metformin</td>
<td>↑ AMP kinase</td>
<td>↓ LFTs and insulin resistance</td>
<td>+/-- improvement in steatosis, inflammation, and fibrosis</td>
<td>Data conflicting; no RCTs</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>↓ Oxidative stress</td>
<td>↓ LFTs</td>
<td>Uncertain</td>
<td>Large trials with histologic follow-up evaluation required</td>
</tr>
<tr>
<td>Betaine</td>
<td>↓ Oxidative stress</td>
<td>↓ LFTs</td>
<td>↓ Steatosis, inflammation, fibrosis</td>
<td>Pilot study only</td>
</tr>
<tr>
<td>UDCA</td>
<td>Hepatoprotective</td>
<td>No change</td>
<td>No change</td>
<td>Not beneficial in large RCT</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Hepatoprotective</td>
<td>↓ LFTs, TNF-α</td>
<td>↓ Steatosis, inflammation</td>
<td>Pilot study only</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>Improve lipid panel</td>
<td>? LFTs</td>
<td>Uncertain</td>
<td>Conflicting studies</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Blocks cholesterol absorption in intestine</td>
<td>? LFTs</td>
<td>↓ Steatosis and fibrosis</td>
<td>Animal data</td>
</tr>
<tr>
<td>Angiotensin-receptor blockers</td>
<td>? Inhibits stellate cells</td>
<td>↓ LFTs</td>
<td>↓ Fibrosis</td>
<td>Animal and pilot studies</td>
</tr>
</tbody>
</table>

\[\text{↓}, \text{ decreases; AMP, adenosine 5'-monophosphate; LFT, liver function test; PPAR, peroxisome proliferator-activated receptor; HMG CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; TNF, tumor necrosis factor.}\]
Collectively these studies support the general concept that slow gradual weight loss through diet and exercise may prove beneficial in the treatment of NASH. Clearly, however, larger RCTs are needed to better define the optimal exercise regimen as well as the most beneficial dietary composition and total calorie intake.

Medical Therapies That Augment Weight Loss

Orlistat. The reversible inhibitor of gastric and pancreatic lipase, orlistat, appears to be the most studied weight loss medication used in the treatment of NASH. This medication is taken with meals and blocks approximately 30% of dietary triglycerides. Early pilot work suggested this medication may be beneficial in the treatment of NASH.113,114 Two subsequent randomized controlled trials were performed to further investigate the potentially beneficial effects of orlistat in the treatment of NASH.115,116 Six to 9 months of therapy with orlistat vs placebo produced 8% vs 6% total body weight loss, respectively. Zelber-Sagi et al115 showed steatosis only improved in the orlistat group despite significant weight loss in each group. Harrison et al116 obtained repeat liver biopsies at 9 months and showed that regardless of regimen, a 9% body weight reduction produced improvement in biochemical markers, serum aminotransferase levels, steatosis, and necroinflammation, but no improvement in fibrosis. The implications of these 2 RCTs were that weight loss is the common pathway through which orlistat may exert a beneficial effect. Other weight loss medications are under investigation in search of a medication with minimal side effects and excellent efficacy. These data, combined with diet and exercise studies, suggest that relatively modest amounts of weight loss, on the order of 5%–10%, will lead to improvement in both biochemical and histopathologic abnormalities seen in NASH.

Rimonabant. Increasing evidence suggests the endocannabinoid system is enhanced in the setting of overweight or obesity. Activation of cannabinoid (CB-1) receptors located both centrally and peripherally (to include organs involved in energy homeostasis such as the liver, adipocytes, and possibly skeletal muscle and pancreas), lead to enhanced weight gain and altered energy metabolism. Inhibition of these receptors has been the subject of recent intense investigation.

Although not specifically studied in NASH patients to date, several large randomized placebo-controlled trials with the cannabinoid-1 antagonist, rimonabant, in both overweight/obese nondiabetic and diabetic patients have been performed.117 Rimonabant given at a dose of 20 mg/day for 1 year is associated with a weight loss of 4.7 to 5.4 kg and improved waist circumference. Significant improvement in serum triglyceride levels, HDL levels, insulin resistance, and adiponectin levels also has been shown and seem to be greater than what would be expected with weight loss alone, suggesting an added peripheral effect. In addition, significant improvement in serum ALT levels, γ-glutamyltransferase levels, alkaline phosphatase levels, and hepatic steatosis has been shown in an animal model of NAFLD.118 Multicentered RCTs of rimonabant in human beings with NASH are underway. The recent association of this medication with psychiatric issues to include depression may limit its future use, and it is currently not available in the United States outside of clinical research trials.

Glucagon-like protein-1–receptor agonist (incretin analogs). Peptides that are derived from glucagon-like protein-1–receptor agonists such as exenatide also may prove to be potential therapeutic agents in the treatment of NASH. These incretin analogs have been studied extensively in patients with type 2 diabetes mellitus and have been found to promote insulin secretion, suppress inappropriate glucagon secretion, slow gastric emptying, induce satiety, and are associated with modest weight loss. Nausea occurs in up to 57% of patients, typically early in the course of therapy, and can be mitigated with dose titration.119 A recent study in obese mice showed reduced markers of oxidative stress and insulin resistance as well as decreased hepatic steatosis.120 A recent case report of a diabetic male patient with NAFLD treated for 44 weeks with exenatide showed improvement in serum aminotransferase levels and hepatic steatosis.121 Numerous other studies have supported the glycemic benefits of exenatide (exendin-4) with further well-designed studies specific to NASH populations required.

Surgical Therapy for Weight Loss

Until medical therapy is developed that effectively promotes and sustains weight loss, surgical therapy will continue to remain a viable alternative in select patient populations. Surgical therapy for obesity has become exceedingly popular in the past decade and has evolved significantly from the early malabsorptive surgeries. These early surgeries such as the jejunoileal bypass produced dramatic weight loss but were shown to cause significant worsening of liver disease postoperatively.122,123 Newer surgical techniques such as adjustable gastric banding and Roux-en-Y gastric bypass are overall better tolerated and have been shown to improve metabolic syndrome, insulin resistance, and hepatic histology.

Adjustable gastric banding in 22 obese NASH patients produced an average 34-kg weight loss as well as significant improvement in hepatic steatosis, inflammation, and fibrosis at repeat liver biopsy more than 2 years after surgery.52 Roux-en-Y gastric bypass has been used to produce even greater weight loss and its utility in improving NASH has been well studied. A recent study of 19 morbidly obese NASH patients who lost a mean of 52 kg of body weight after Roux-en-Y gastric bypass showed significant improvement in steatosis, lobular inflammation, and fibrosis on average 21.4 months postoperatively.83 Another study of 70 patients undergoing bariatric
surgery showed a mean weight loss of 59% at 15 months after surgery and 82% improvement in steatohepatitis and 39% improvement in fibrosis.124 Others also have shown large metabolic and histologic improvements post–gastric bypass with no patients showing worsening of hepatic fibrosis and 50%–75% of patients showing improvement in hepatic fibrosis.125,126 These studies provide compelling evidence that bariatric surgery, using either adjustable gastric banding or Roux-en-Y gastric bypass, results in substantial weight loss, and is associated with a marked improvement in biochemical and histologic parameters of NASH patients. Subsequently, these invasive therapies should be considered in morbidly obese patients with other medical conditions that cumulatively would warrant the risks of surgical intervention.

**Medical Therapies That Improve Metabolic Profiles**

In a similar manner to the tests under development using specific biomarkers to diagnose NASH based on a common pathway of insulin resistance and oxidative stress, pharmacologic therapies have been evaluated that have targeted these same pathways. As the steps involved in the development of steatohepatitis and fibrosis are elucidated further, pharmacologic therapies may be better directed to cause histologic and biochemical improvement.

**Insulin-Sensitizing Medications**

**Thiazolidinediones.** Thiazolidinediones (TZDs) improve insulin resistance in skeletal muscle, adipose tissue, and the liver through their action as peroxisome proliferator–activated receptor γ agonists that increase plasma adiponectin levels and fatty acid oxidation and decrease fatty acid synthesis.127 These agents have been the most studied insulin sensitizers used in the treatment of NASH. Pioglitazone and rosiglitazone are the 2 currently available TZDs and both have been evaluated in small prospective trials.

A preliminary study of 22 NASH patients (~50% with impaired glucose tolerance or diabetes) treated for 48 weeks with rosiglitazone showed overall improvement in insulin sensitivity and serum aminotransferase levels. Repeat liver biopsy at 48 weeks showed significant improvement in necroinflammation, ballooning, and zone 3 perisinusoidal fibrosis with 45% (10 patients) no longer meeting criteria for NASH. However, this study lacked a control arm and within 6 months posttherapy serum aminotransferase levels were almost back to pretreatment levels.128 A subsequent randomized, placebo-controlled trial in 63 NASH patients (32% with diabetes) treated for 1 year with rosiglitazone 8 mg/day showed significantly greater improvement in steatosis compared with placebo, and significantly less histologic progression in reference to ballooning, inflammation, and fibrosis.129 However, improvement in steatosis was not seen uniformly in all patients treated with rosiglitazone.

Pioglitazone also was evaluated in several small pilot and proof-of-concept trials. An open-label trial in 18 nondiabetic NASH patients treated with 30 mg/day for 48 weeks showed overall histologic improvement in two thirds of patients with significant improvement in steatosis, cellular injury, parenchymal inflammation, and fibrosis.130 Another pilot study compared pioglitazone 30 mg/day plus vitamin E 400 IU/day with vitamin E alone and showed improvement in steatosis in both groups but improvement in hepatic inflammation and fibrosis in the pioglitazone plus vitamin E arm only.131 A more recent placebo-controlled study by Belfort et al132 in 55 NASH patients with impaired glucose tolerance or type 2 diabetes mellitus provided evidence that therapy with 6 months of a low-calorie diet plus pioglitazone improved biochemical and histologic parameters significantly more than patients prescribed a low-calorie diet and placebo. Although significant improvement was seen for steatosis and inflammation compared with placebo, fibrosis improvement did not reach significance when compared with the placebo group (P = .08). These preliminary findings are supported by another randomized placebo-controlled trial that followed up 74 nondiabetic patients for 12 months and showed significant improvement in metabolic and histologic parameters, including fibrosis, in the pioglitazone group when compared with placebo.133 Interestingly, lobular inflammation and steatosis were not improved between groups and further investigation is necessary to understand these findings.

Although these studies provided some evidence that the TZDs may be beneficial in the short term, the long-term benefits remain to be seen. Lutchman et al134 showed that continued therapy may be required to maintain histologic benefit. In this study of 21 patients treated for 48 weeks with pioglitazone, liver biopsies were performed at baseline, at end of therapy, and, in 9 patients, 48 weeks after stopping therapy. In the patients who underwent the 3 serial liver biopsies, initial improvement in biochemical and histologic parameters were not maintained at the 48-week posttherapy evaluation, with 7 of 9 patients developing histopathologic evidence of NASH once again, despite no change in average body weight.

The side-effect profile of the TZD class of medication also must be addressed. Modest weight gain of approximately 2–3 kg has been shown routinely and appears to be caused by increased peripheral fat deposition. Some retrospective studies also suggest that TZDs promote bone loss and may contribute to osteoporosis and increased fractures, particularly in postmenopausal women.135 If limited durations of therapy were adequate, this would be less of an issue, but if long-term therapy is necessary to maintain hepatic benefit, this must be better addressed. Further investigation is required to definitively address this issue.
Moreover, a recent meta-analysis of diabetic male patients taking rosiglitazone has suggested an increased risk of cardiovascular events.\textsuperscript{136} Although this study tabulated an increased risk of myocardial infarction of 43% and cardiovascular death of 64%, it has been widely criticized for its inclusion criteria, methods of statistical analysis, and overall low event rate.\textsuperscript{137} Other analyses using broader inclusion criteria and different statistical analysis failed to show a significant increase in myocardial infarction in this same patient population. Furthermore, a similar meta-analysis with pioglitazone showed a 20% reduction in cardiovascular events.\textsuperscript{138} Additional investigation is required to address the issue definitively.

The risk of congestive heart failure exacerbation with the use of TZDs also has been reported and has been attributed to TZD-related fluid retention and diastolic dysfunction in susceptible individuals. Subsequently these agents are contraindicated in patients with New York Heart Classification stage 3–4 heart failure. Lago et al\textsuperscript{139} recently showed an increased risk of congestive heart failure, but did not show increased cardiovascular death among patients taking TZDs. Large prospective trials are ongoing and their results will determine the future of TZDs in the treatment of NASH.

**Metformin.** Metformin is a biguanide that improves insulin sensitivity by decreasing hepatic gluconeogenesis and limiting triacylglycerol production. Animal model data has been promising, with early studies of obese mice given metformin showing improved serum transaminase levels, hepatomegaly, and steatosis.\textsuperscript{140} Data from human studies are limited. Marchensini et al\textsuperscript{141} first showed improvement in insulin sensitivity and serum aminotransferase levels in an open-label trial of 20 patients treated with metformin 1500 mg/day for 4 months. This was followed by a 6-month randomized open-label trial of metformin 850 mg twice daily plus diet vs dietary restriction of 1600 to 1800 kcal/day.\textsuperscript{142} Significant improvement was seen in the metformin group compared with the diet-alone group. However, no significant improvement in necroinflammation or fibrosis was found. A similar open-label trial of metformin given for 1 year in 15 patients showed improvement in serum aminotransferase levels and insulin sensitivity at 3 months, but return of serum aminotransferase levels to pretreatment levels were seen by the completion of the study.\textsuperscript{143}

A subsequent open-label RCT in 110 NAFLD patients was performed in Italy that compared metformin treatment with 2 control groups of vitamin E 800 IU/day or a prescriptive, weight-reducing diet.\textsuperscript{144} Metformin showed higher rates of aminotransferase normalization. Repeat liver biopsy in 31% of the metformin group showed improvement in steatosis, necroinflammation, and fibrosis, although there was no histologic follow-up evaluation in the control groups. Interestingly, metformin compared with rosiglitazone in a study of 20 patients with type 2 diabetes showed improvement in insulin resistance and transaminase levels in both groups but decreased hepatic fat as measured by proton spectroscopy in the rosiglitazone group.\textsuperscript{145}

Overall, the insulin-sensitizing medications show the most promise to date in improving histopathology in patients with NASH. Current data suggest that metformin may be less efficacious than the TZD class of medications; however, randomized, placebo-controlled studies with metformin using histopathologic end points have yet to be performed. Interestingly, one difference between the 2 classes of insulin sensitizers is the ability of the TZD class to up-regulate adiponectin expression. Given the multiple effects of adiponectin including up-regulation of adenosine 5′-monophosphate (AMP) kinase and peroxisome proliferator–activated receptor-α inhibition, the inability of metformin to positively impact adiponectin expression may have important consequences on the overall effectiveness of this medication in the treatment of NASH, at least when used as monotherapy. Combination therapy with metformin and the TZD class of medications deserves consideration in clinical trials because the untoward weight gain with TZD monotherapy may be mitigated.

**Antioxidant therapy.** The depletion of antioxidants within hepatocytes resulting in impaired ROS inactivation is the basis for antioxidant supplementation as a potential treatment for NASH.\textsuperscript{146} The lipid-soluble antioxidant, α-tocopherol (vitamin E), has been shown to inhibit lipid peroxidation and suppress inflammatory cytokines such as tumor necrosis factor-α, and its use in the treatment of NASH has been studied. One study comparing 6 months of 1000 IU vitamin E and 1000 mg vitamin C daily vs placebo showed significant improvement in hepatic fibrosis within the vitamin group but not between groups and no change in serum aminotransferase levels or hepatic inflammation.\textsuperscript{147} Alternatively, others have shown improvement in serum aminotransferase levels and insulin resistance although follow-up histopathology was not assessed.\textsuperscript{148,149}

Betaine, another antioxidant studied in the treatment of NASH, increases S-adenosylmethionine levels and is thought to reduce fat deposition in the liver.\textsuperscript{143} Marked improvement in serum aminotransferase levels, hepatic steatosis, inflammatory activity, and fibrosis was seen in a pilot trial of 10 NASH patients treated with betaine anhydrous in a 20-mg divided dose daily for 12 months.\textsuperscript{150} Rigorous follow-up studies are required with particular attention paid to the formulation of betaine used because betaine anhydrous is a medication regulated by the Food and Drug Administration whereas the more readily available betaine hydrochloride is a dietary supplement found in nutrition stores.\textsuperscript{151}

Phlebotomy targeting hepatic iron overload with resultant increased oxidative stress is another potential therapeutic modality that has been investigated in the
treatment of NASH. In a study of 64 NAFLD patients undergoing therapeutic phlebotomy to a goal of a ferritin level of less than 80 ng/mL for 8 months in addition to lifestyle modification vs lifestyle modification alone, the phlebotomy group showed significantly improved insulin resistance. Serum aminotransferase levels were not significantly different between the 2 groups and hepatic histology was not assessed in this preliminary study. Larger studies with histologic follow-up are necessary to determine the utility of this treatment modality.

Overall, antioxidants represent a novel class of medications that have shown some promising initial results in the treatment of NASH but further well-designed large RCTs are required and it is likely that these therapies will be used in combination regimens with other agents that affect insulin sensitivity.

Others

Cytoprotective agents. Cytoprotective agents are thought to work by preventing apoptosis and down-regulating the inflammatory cascade that has been shown to occur in NAFLD patients. Ursodeoxycholic acid (UDCA) is the most studied and initial pilot trials proved promising as a NASH-specific therapy. However, a well-conducted, multicenter, double-blind, placebo-controlled trial of UDCA for 2 years failed to show significant change in biochemical or histologic parameters. Interestingly, Dufour et al showed biochemical benefit as well as reduced steatosis with the combination of UDCA with vitamin E compared with UDCA plus placebo or double-placebo groups after 2 years of therapy. It remains to be seen whether UDCA in combination with other medications may prove clinically efficacious.

Pentoxifylline, another cytoprotective agent, exerts its effect through inhibition of tumor necrosis factor-α. Twelve months of pentoxifylline 400 mg 3 times daily given in 2 recent pilot trials improved serum aminotransferase levels as well as steatosis and lobular inflammation. Although no dangerous side effects have been noted, the high rates of nausea with this medication resulting in a 50% drop-out rate may limit the clinical utility of this medication.

3-hydroxy-3-methylglutaryl coenzyme A reductase therapy. Medications that exert beneficial effects on lipid profiles offer another potential therapeutic class of medications. The most studied of this family of lipid-lowering medicines are the statins, which work through inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, which catalyses an essential step in cholesterol biosynthesis. Initially statins were noted to cause increases in hepatic transaminase levels in patients when used to treat hyperlipidemia, and therefore were thought to be harmful to liver function. However, recent studies have shown statins to be safe when given to patients with NAFLD. An early pilot trial with atorvastatin raised interest in using statins to treat NASH, but a more recent study with simvastatin showed no affect on adiponectin or improvement in insulin sensitivity in a group of patients with metabolic syndrome. Questions remain in reference to the specific mechanisms of action of these drugs and it may be that they have positive effects beyond altering insulin sensitivity or adipocytokine levels, but these studies have yet to be performed.

Ezetimibe. Ezetimibe (Zetia, Kenilworth, NJ) is another lipid-lowering medication that may have hepatic benefits in the treatment of NASH. This medication selectively inhibits intestinal cholesterol absorption and in controlled studies with statins appears to lower serum LDL cholesterol by 24% as well as triglycerides by 16%. A recent study by Deushi et al showed improved insulin resistance and decreased lipid deposition and fibrosis in obese rats treated with ezetimibe. No clinical trials with this therapy have been published.

Angiotensin-receptor blockers. A novel class of medications that have been evaluated in the treatment of NASH are the angiotensin-receptor blockers. These medications, which have been used to treat hypertension and congestive heart failure, have been shown to have liver-specific beneficial effects. Obese mice given angiotensin-receptor blockers showed improved serum aminotransferase levels and reduced expression of inflammatory cytokines and hepatic fibrosis through inhibition of hepatic stellate cell activity. Two human pilot studies also have been completed and suggest that angiotensin-receptor blockers may improve serum aminotransferase levels and provide histologic benefit in NASH patients. Similar to most of the research conducted in regards to NASH therapy, large placebo-controlled RCTs are required to ascertain if any substantial benefit can be achieved with long-term angiotensin-receptor blocker therapy in NASH patients.

Conclusions

The myriad of public health issues related to the obesity epidemic continues to grow as more medical conditions are linked to obesity, insulin resistance, and the metabolic syndrome. The growing incidence of NAFLD, and subsequently NASH, almost certainly will be reflected in subsequent increases in cirrhosis and hepatocellular carcinoma in the future. Noninvasive and accurate screening tests to correctly identify patients at risk for disease progression as well as effective treatment regimens must be developed for these high-risk patients. Currently, there is no ideal treatment regimen but those interventions that produce sustained substantial weight loss such as bariatric surgery seem to provide the single most benefit. Modest but sustained weight loss, regular exercise, and diet composition modification also appear to ameliorate biochemical and histologic abnormalities.

Thus far, medical therapies with the exception of the TZDs have not been subjected to randomized, placebo-
controlled trials and have shown only modest preliminary benefits. The TZDs, although appearing to be effective in reducing steatosis, inflammation, and fibrosis are limited by small proof-of-concept trials and potentially untoward effect profiles as well as an apparent need for maintenance therapy. Other therapies directed at insulin resistance, oxidative stress, cytoprotection, and fibrosis also may offer benefit, but further study is required. A multifaceted approach that relies on lifestyle changes, limited weight loss, and pharmacotherapy requires further investigation because no one treatment approach has proved universally applicable to the large general population with NASH.

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Address requests for reprints to: Stephen A. Harrison, MD, Department of Gastroenterology, 3851 Roger Brooke Drive, Fort Sam Houston, Texas 78234. e-mail: stephen.harrison@amedd.army.mil; fax: (210) 916-5611.

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