

# Non-alcoholic fatty liver disease: What's in our arsenal?

Lifestyle changes and metabolic syndrome management are the best interventions for NAFLD. Less clear is which agents to use for liver-directed pharmacotherapy.

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## PRACTICE RECOMMENDATIONS

- › Screen patients with non-alcoholic fatty liver disease (NAFLD) for type 2 diabetes mellitus. **A**
- › Treat components of the metabolic syndrome to improve the clinical outcome in patients with NAFLD. **A**
- › Consider liver-directed pharmacotherapy, such as antioxidants (eg, vitamin E), insulin sensitizers, bile acid sequestrants, and pentoxifylline, to treat severe NAFLD. **B**

### Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

**CASE** ▶ A 39-year-old Hispanic man with a body mass index (BMI) of 35 kg/m<sup>2</sup>, type 2 diabetes mellitus (T2DM), and hypertension is referred for evaluation of abnormal liver function tests (LFTs) and fatty liver on ultrasound. He is taking metformin and lisinopril, and a patient alcohol screening survey is negative. LFT results reveal the following: alanine aminotransferase (ALT) 27 IU/dL; aspartate aminotransferase (AST) 43 IU/dL; albumin 4.2 g/dL; gamma glutamyl transferase 22 u/L; alkaline phosphatase 51 IU/L; and total bilirubin 0.3 mg/dL. Lactate dehydrogenase and prothrombin time are normal.

Results of his liver screen are as follows: hepatitis B surface antigen, hepatitis C antibody, antimitochondrial antibody, and anti-smooth muscle antibody are negative, and iron, transferrin saturation, and ceruloplasmin are in normal range. Antinuclear antibody (1:20 dilution) is weakly positive, and alpha-1 antitrypsin (264 mg/dL) and serum ferritin (300 ng/mL) are mildly increased.

The patient undergoes a liver biopsy that shows grade 2 steatosis, grade 1 lobular inflammation, few ballooned hepatocytes, and stage 1 fibrosis. Based on these clinical findings, he is given a diagnosis of non-alcoholic fatty liver disease (NAFLD).

**N** AFLD is the most frequent cause of chronic liver disease both in the United States and globally.<sup>1</sup> In fact, a number of long-term epidemiologic studies report that nearly one-third of the US population has the disease.<sup>2</sup> The spectrum of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) to cirrhosis. Of patients with NAFLD, 10% to 30% have the more severe form—NASH—and about 10% of those with NASH progress to cirrhosis and other liver-related complications.<sup>3</sup>

People with NAFLD consume no alcohol, or only a modest amount (ie, weekly intake <140 g in women and <210 g in men). Typically, they are asymptomatic with normal or mildly abnormal LFTs discovered as part of a preventive health

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screening. In patients with simple hepatic steatosis alone, serum ALT levels are higher than serum AST levels. (In contrast, patients with alcoholic liver injury and NASH with progressive fibrosis have higher serum AST than ALT levels.) A serum hepatitis panel and liver screen are negative for other explanations of chronic liver disease.

NAFLD is strongly associated with obesity, insulin resistance/T2DM, and hyperlipidemia, all of which are components of metabolic syndrome. Obesity, particularly central obesity, is highly predictive of hepatic steatosis and disease progression.<sup>4</sup> T2DM occurs 5 to 9 times more frequently in people with NAFLD than in the general population,<sup>5</sup> and, conversely, nearly 66% of patients with T2DM have NAFLD.<sup>6,7</sup> Furthermore, nearly 70% of patients with T2DM develop fatty liver and its consequences, including NASH, fibrosis, cirrhosis, and hepatocellular carcinoma.<sup>5,7</sup>

**■ 4 therapeutic strategies.** Based on our current understanding of the pathogenesis of NAFLD, there are 4 main therapeutic avenues: lifestyle modification, liver-directed pharmacotherapy, management of metabolic syndrome, and surveillance of the complications of cirrhosis. The review that follows explores the evidence to date for each.

### **Take steps to reduce weight and increase physical activity**

The primary objective with NAFLD is to right the imbalance between calorie intake and utilization so as to reverse the obesity and insulin resistance underlying the disease.

**■ Target carbohydrates.** Current data clearly suggest that energy intake is significantly higher in patients with NAFLD than in those without the disease.<sup>8</sup> Thus, reducing dietary carbohydrate and overall energy intake is beneficial to preventing and halting the progression of liver damage. Increased intake of high fructose corn syrup may be at least partially to blame; research has linked the substance to the occurrence of obesity, metabolic syndrome, and NAFLD.<sup>9</sup>

The optimal diet to treat NAFLD is not known because of the difficulties inherent to performing well-designed dietary inter-

vention trials and ensuring long-term compliance. At least one study reported that a Mediterranean diet helped reduce hepatic steatosis and improve insulin sensitivity in nondiabetic individuals.<sup>10</sup> Generally, patients should avoid saturated fats, simple carbohydrates, and sweetened drinks, and they should be instructed to restrict calories to cause weight loss of about .5 kg to 1 kg per week until the target weight is achieved.<sup>11</sup>

Current observational studies indicate that prudent calorie restriction combined with increased physical activity is the best strategy for achieving and sustaining optimum body weight; severe calorie restriction is likely to cause skeletal muscle loss that can aggravate NAFLD.

**■ Encourage exercise.** Aerobic exercise improves skeletal muscle insulin sensitivity—the primary underlying mechanism that causes NAFLD.<sup>12</sup> Although the optimum duration and intensity of exercise is not known, several randomized controlled trials (RCTs) found that moderately intense training, high-intensity training, and/or resistance training improved hepatic steatosis and insulin resistance, but an effect on ALT was inconsistent.<sup>13</sup> (None of these studies included histology as an outcome measure.)

Given the multitude of benefits of aerobic exercise, there is no question that patients with NAFLD should try to increase their physical activity and incorporate exercise into their daily routine.

**■ Hold off on pharmacologic weight loss.** Orlistat, an enteric lipase inhibitor, causes malabsorption of dietary fat, which leads to weight loss. Although one study demonstrated that orlistat improves ALT and steatosis in patients with NAFLD, a subsequent RCT concluded that orlistat with caloric restriction and vitamin E (800 IU/d) did not enhance weight loss over caloric restriction and vitamin E alone.<sup>14</sup> Additionally, in patients with weight loss >9% of body weight, histologic improvement occurred independent of orlistat.<sup>14</sup> Therefore, orlistat is not currently recommended for weight loss in patients with NAFLD.

**■ Keep bariatric surgery on your radar.** Bariatric-metabolic surgery provides the most reliable method for achieving sustained

weight loss in morbidly obese individuals with NAFLD. Commonly used surgical procedures are associated with reduced steatosis and lobular inflammatory changes, but reports are conflicting regarding fibrosis.<sup>15</sup>

The majority of published data indicate that bariatric surgery improves the histologic and metabolic changes associated with NAFLD and has potential as a treatment option for patients with morbid obesity and NAFLD. However, the timing and type of surgery that is most effective, and whether bariatric surgery can cure the disease, remain unanswered questions. Long-term follow-up and RCTs are needed to address these issues. As a result, no definitive recommendations regarding bariatric surgery as a treatment for NAFLD can be made at this time.<sup>15</sup>

### Liver-directed pharmacotherapy: Evidence is lacking for many agents

Lifestyle modification remains the mainstay of therapy for NAFLD because of its efficacy and lack of adverse effects. But low compliance rates often make pharmacotherapy necessary to reduce the health burden related to NAFLD. Despite the success rate of pharmacologic agents that focus on insulin resistance and lipid metabolism and that have antioxidant properties, the long-term safety and efficacy of many of these agents is largely unknown. Furthermore, the FDA has not approved any pharmacologic agents specifically for the treatment of NAFLD. Here's what we know:

■ **Vitamin E.** Five RCTs have evaluated the antioxidant vitamin E in patients with NASH. The best study published to date found that 96 weeks of therapy with 800 IU/d vitamin E was associated with a 42% improvement in hepatic histology, compared with 19% improvement in the placebo group.<sup>16</sup> Vitamin E was also associated with improved serum ALT.

Although vitamin E seems to be a promising agent for the treatment of NASH, concerns exist about its long-term safety because of an increased risk of all-cause mortality and hemorrhagic stroke.<sup>17</sup> In addition, because the optimal dose and duration of treatment is unknown and because studies have not

evaluated the supplement in patients who have diabetes and NASH, vitamin E is not currently considered to be a standard therapy for NASH.

■ **Insulin sensitizers.** Because insulin resistance is believed to be the underlying mechanism for the development and progression of NAFLD, a compelling rationale exists for the use of insulin sensitizers in the management of the disease. Metformin, an activator of adenosine monophosphate-activated protein kinase, and the thiazolidinediones (pioglitazone and rosiglitazone) are the most extensively studied agents in clinical trials. A number of studies looking at the effects of metformin on NAFLD found that liver function, steatosis, and insulin sensitivity improved;<sup>18</sup> however, a recent meta-analysis found that metformin failed to improve liver histology.<sup>19</sup>

Similarly, although clinical trials have shown that thiazolidinediones improve liver enzymes, inflammatory markers, and hepatic steatosis, questions surround their long-term safety.<sup>20</sup> The largest placebo-controlled trial on this issue to date—PIVENS (pioglitazone vs vitamin E vs placebo)—found that pioglitazone was beneficial in improving hepatic histology.<sup>16</sup> However, the well-recognized adverse effects of pioglitazone (eg, upper respiratory tract infection, edema, and hypoglycemia) may temper its utility.

Clinical trials involving newer anti-diabetic agents, such as dipeptidyl peptidase-4 (DPP4) inhibitors and glucagon-like peptide-1 (GLP1) analogues, indicate that such agents improve insulin resistance, steatosis, and inflammation.<sup>21</sup> However, these drugs are not considered to be routine therapy because of limited data and the lack of long-term benefits.

■ **Bile acid regulatory agents.** Ursodeoxycholic acid (UDCA), a bile acid with antiapoptotic and cytoprotective properties, is used as a hepatoprotectant in NAFLD. Although early studies showed no significant differences in LFT results between UDCA-treated and untreated groups, recent RCTs indicate that UDCA improves ALT and serum fibrosis.<sup>22,23</sup> The FLINT trial, a recent multicenter RCT involving obeticholic acid, found that UDCA was associated with improvement in histologic



Although vitamin E appears promising for the treatment of non-alcoholic steatohepatitis, concerns exist about the increased risk of all-cause mortality and hemorrhagic stroke.

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outcomes, although long-term benefits and safety—especially with regard to worsening hyperlipidemia—are questionable.<sup>24</sup>

■ **Pentoxifylline.** Researchers have evaluated pentoxifylline, a hepatoprotectant with anti-tumor necrosis factor effect, in the treatment of NAFLD.<sup>25</sup> In fact, pooled results from 5 well-designed studies indicate that pentoxifylline significantly reduces ALT and AST and improves steatosis, lobular inflammation, and fibrosis.<sup>26</sup> Although these data suggest that pentoxifylline holds promise as a therapeutic option, the lack of large multicenter studies and FDA approval temper its utility in the management of NASH at this time.

■ **Cholesterol-lowering agents.** Statins inhibit hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase in the liver and have anti-inflammatory and anti-fibrogenic properties. They have been used in patients with NAFLD, primarily because of their cardiovascular benefit. Two RCTs with high risk of bias and a small number of participants found statin therapy to be associated with improved serum transaminases and ultrasound findings; however, liver biopsies were not performed in either of these studies.<sup>27</sup>

Lowering cholesterol using an absorption inhibitor, such as ezetimibe, was associated with improvement in liver histology in a single RCT.<sup>28</sup> Even though statins are not considered to be a treatment for NAFLD, they can be used to safely lower plasma cholesterol in patients with the disease.

■ **Renin-angiotensin system (RAS) inhibitors.** Research in animals indicates that activation of the renin-angiotensin system contributes to the pathogenesis of NAFLD, but data on the benefits of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with NAFLD are limited, conflicting, and derived largely from retrospective<sup>29</sup> and pilot prospective studies.

Based on currently published literature, RAS inhibitors are not considered an NAFLD treatment. However, because cardiovascular disease is a major cause of death in patients with NAFLD, the renal and cardiovascular protection offered by these agents likely lowers mortality in patients with the disease.

■ **Probiotics.** The use of probiotics in the

treatment of NAFLD is based on the premise that alterations in intestinal microbes and the inflammatory response may improve the disease. Three RCTs involving different formulations of probiotics, synbiotics, or placebo, showed improvement in serum liver markers and insulin resistance, but did not include histologic outcome measures.<sup>30</sup> Furthermore, the long-term consequences of altered gut flora are presently unknown. As such, the available evidence does not support the use of probiotics for the treatment of NAFLD.

■ **Polyunsaturated fatty acids (PUFA).** Clearly, omega-3 fatty acids have beneficial effects on cardiometabolic risk factors and positively impact lipid metabolism and insulin sensitivity. In addition, a few studies have reported improvement in non-histologic outcome measures of NAFLD, but 2 high-quality RCTs found no benefit of fish oil-based PUFA on histology.<sup>31,32</sup> Thus, current evidence does not support recommending PUFA supplementation for the treatment of NAFLD.

■ **Chinese herbal medicines.** At least 56 trials have looked at 75 different Chinese herbal medicines in varying formulations, dosages, routes of administration, and durations of treatment, using various controlled interventions.<sup>33</sup> No trial reported primary outcomes, such as hepatic-related mortality, morbidity, or health care quality of life. Although a large number of the trials reported some positive effects on various biochemical or radiologic measures, the high risk of bias and the limited number of trials testing individual herbal medicines leave efficacy and safety open to question. As such, no Chinese herbal medicines are regarded as treatment for NAFLD at this time.

### Target components of metabolic syndrome

Management of the components of metabolic syndrome remains one of the safest and most effective ways to manage NAFLD. Therefore, screening for and treating T2DM, hypertension, and dyslipidemia are priorities. Although obstructive sleep apnea (OSA) is not part of metabolic syndrome, the condition frequently coexists with metabolic syndrome because both entities have obesity as a risk factor.

■ **T2DM.** Screen all patients with NAFLD for T2DM and vice-versa because, as noted earlier, patients with diabetes have more severe and progressive NAFLD, and a high proportion of patients with NAFLD have T2DM.<sup>5,6</sup> Although research has not shown metformin to improve histology in NASH, metformin is recommended as a first-line agent for the treatment of T2DM because it aids in weight loss and lowers diabetes-related mortality.<sup>34</sup>

Pioglitazone is considered a second-line agent. Despite its beneficial effects on insulin sensitivity and hepatic histology, there are concerns about the adverse effects of thiazolidinediones. GLP1 analogues, which improve liver enzymes and reduce hepatic steatosis, are considered third-line agents.

■ **Hypertension.** Because approximately 70% of patients with NAFLD have hypertension,<sup>35</sup> it is imperative to screen patients for the condition. If blood pressure is >140/90 mm Hg, patients should be managed according to hypertension guidelines. ACE inhibitors or ARBs are recommended as first-line therapy, since blocking the renin-angiotensin system potentially reduces hepatic fibrosis,<sup>36</sup> and ARBs may lower transaminases and improve insulin sensitivity in NAFLD.

■ **Dyslipidemia.** Treatment of dyslipidemia is essential to lowering cardiovascular mortality in patients with NAFLD. Even though elevated transaminases occur with NAFLD, this should not preclude starting therapy to lower triglycerides to <150 mg/dL and total cholesterol to <200 mg/dL.

■ **OSA.** Because of the high prevalence of OSA in patients with NAFLD, physicians should have a high index of suspicion and screen this population for sleep disorders. OSA is associated with an increased risk of NAFLD and advanced fibrosis in NASH.<sup>37</sup> Treatment of OSA improves quality of life and controls blood pressure in patients with NAFLD, but it's currently unclear whether targeting sleep disorders can slow the progression of fibrosis in NAFLD.

### Concentrate on the complications of cirrhosis

Patients with NASH cirrhosis, like those with cirrhosis of other etiologies, are at risk for

complications, including hepatic encephalopathy, ascites, hepatorenal syndrome, and esophageal variceal hemorrhage. Surveillance to detect these include an annual liver ultrasound, an alpha-fetoprotein test every 6 months, esophagogastroduodenoscopy for varices, and an assessment for liver transplantation. For more on these complications, see, "Cirrhosis complications: Keeping them under control," *J Fam Pract.* 2015;64:338-342. NAFLD-associated cirrhosis is the third most frequent indication for liver transplantation in the United States and may become the most frequent indication in the next decade.<sup>38</sup>

**CASE ►** Because the patient's liver biopsy showed early NASH, we recommended that he aggressively pursue lifestyle modification, including regular physical activity and dietary changes. Additionally, we discussed optimization of glycemic control and continued use of lisinopril for control of hypertension. On follow-up 6 months later, he had lost weight and his BMI was 32 kg/m<sup>2</sup>. In addition, his transaminase levels had improved, but they had not normalized.

We recommended that he continue the same measures, with follow-up every 6 months to ensure compliance with lifestyle modifications and with diabetes and hypertension control. **JFP**

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► Although numerous trials have explored the use of Chinese herbal medicines for non-alcoholic fatty liver disease, the high risk of bias leaves their safety and efficacy open to question.

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