Overview of Nonalcoholic Fatty Liver Disease

Background
Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world, affecting up to 100 million Americans.\(^1\,2\) Severity ranges from mild disease with steatosis (buildup of fat in the liver) to more severe disease with inflammation and hepatocyte (liver cell) injury known as nonalcoholic steatohepatitis (NASH).\(^1\) NASH is projected to be the leading liver transplant indication by the year 2020.\(^1\) The most common cause of death in patients with NAFLD is a cardiovascular cause.\(^3\) As evidence-based therapies for NAFLD, including NASH, are just now emerging, therapy has historically targeted comorbid conditions to reduce cardiovascular risk. This article reviews the utility and safety of therapies to treat NASH, as well as associated comorbid conditions.

Causes and Diagnosis
The exact cause of NAFLD is not known. However, NAFLD is often associated with metabolic conditions such as high cholesterol, hyperglycemia (including prediabetes and type 2 diabetes), insulin resistance, and obesity.\(^4\) These conditions are not only common in patients with NAFLD, but are also believed to increase the risk of developing NAFLD.\(^3\) These conditions increase fat deposits within the liver. In some patients (about 20\%) this steatosis progresses to NASH. About 30\% to 40\% of patients with NASH develop fibrosis while about 20\% develop cirrhosis.\(^2\,4\,5\) Concomitant NAFLD and type 2 diabetes may be associated with an increased rate of progression to more severe disease, including NASH, cirrhosis, and hepatocellular carcinoma.\(^6\)

The following criteria must be met for a diagnosis of NAFLD:\(^7\)

- Hepatic steatosis (>5\% by histology or >5.6\% by nuclear techniques)
- Limited alcohol consumption, defined as <21 drinks/week (men) or <14 drinks/week (women).
- Excluding other causes of steatosis (e.g., hepatitis C, medications [e.g., amiodarone, methotrexate], parenteral nutrition).

Signs and Symptoms
Patients with NAFLD are often asymptomatic. It is not routinely screened for, but can be identified after a negative workup for abnormal LFTs or detection of steatosis during an abdominal scan.\(^3\) If signs and symptoms are present, they may include elevated liver enzymes (up to five times the upper limit of normal), an enlarged liver, fatigue, or abdominal pain.\(^1\,4\) For patients with more severe disease (e.g., NASH, cirrhosis), signs and symptoms may include ascites (abdominal swelling), esophageal varices (dilated veins in the esophagus), lower extremity edema, enlarged breasts (men), enlarged spleen, spider-like blood vessels visible through the skin, jaundice (yellowing of the eyes and skin), itching, and confusion.\(^4\,8\)

Lifestyle Changes
Lifestyle modifications including weight loss, diet, and exercise (with weight loss being the most impactful) are recommended in patients with NAFLD.\(^3\) To date, no specific diet can be recommended, as data are lacking to indicate one particular diet is associated with better outcomes compared to another.\(^3\) In addition, the goal intensity and duration of exercise are not well established.\(^3\) However, combining some type of calorie-restriction diet (reducing caloric intake by about 500 to 1,000 calories per day) and exercise appears to be the most effective way to achieve sustained weight loss.\(^3\) Weight loss of 3\% to 5\% has been associated with improved steatosis, while weight loss of about 7\% to 10\% has been associated with improved fibrosis [Evidence level C].\(^3\,6\) Recommend that patients with NAFLD avoid heavy alcohol consumption, defined as more than 14 drinks/week for men and more than 7 drinks/week for women.\(^3\) Some clinicians go beyond this and recommend limiting consumption to no more than one drink per day. In addition to
lifestyle modifications, metabolic conditions and cardiovascular risk factors should be managed.

**Antihypertensives Medications**

It is well established that high blood pressure leads to adverse cardiovascular outcomes. Therefore, blood pressure control is important to minimize cardiovascular risk in patients with NAFLD. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly used in patients with concomitant type 2 diabetes, for renoprotection. Preliminary, small, uncontrolled studies suggest that ACEIs and ARBs may prevent liver fibrosis. However to date, data do not clearly support one particular medication or class of medications over another when controlling blood pressure in patients with NAFLD.

**Diabetes Medications**

Similar to hypertension, type 2 diabetes is a known risk factor for cardiovascular disease. Metformin is considered first-line in the management of diabetes for most patients, including those with mild NAFLD and NASH. In fact, several studies have shown liver enzyme reductions and improved insulin resistance with metformin use. However, metformin does not appear to improve liver histology (e.g., steatosis, fibrosis). Thiazolidinediones have also been evaluated in patients with NAFLD, in patients with and without diabetes. To date, rosiglitazone has not shown positive outcomes. However, pioglitazone at doses up to 45 mg/day has been shown to improve liver injury (e.g., lower liver enzymes) and reduce fibrosis is patients with prediabetes or type 2 diabetes and biopsy-proven NASH [Evidence level C]. This has been seen in patients with and without a coexisting diagnosis of diabetes [Evidence level C]. Pioglitazone is associated with adverse effects, including edema, heart failure, possible bladder cancer, and weight gain. Adverse effects and potential benefits should be considered together prior to starting pioglitazone therapy. There are some preliminary data showing liraglutide and ipragliflozin (a sodium-glucose co-transporter 2 [SGLT2] inhibitor not available in the U.S. or Canada) may provide some benefit in patients with NASH. Larger studies are needed to confirm these benefits.

**Hyperlipidemia Medications**

Lipid profiles in patients with NAFLD are typically characterized by elevated triglyceride levels, small dense low density lipoprotein (LDL), and low levels of high density lipoprotein (HDL). Statins are the lipid-lowering agents of choice because of their robust evidence for reducing cardiovascular events, including death. Though liver injury was a concern with statin therapy in the past, several studies have demonstrated their safety in patients with liver disease, even with elevated baseline liver enzyme levels [Evidence level C]. However, statins should be avoided in patients with decompensated cirrhosis. In addition to or instead of statins, fibrates are sometimes used for significantly elevated triglycerides ≥500 mg/dL (~5 mmol/L). However, there’s no good evidence that lowering triglycerides reduces cardiovascular events or prevents pancreatitis.

**Other Therapies**

Oxidative stress may play a role in liver injury in patients with NASH. Vitamin E has been proposed as a possible therapy for NASH due to its antioxidant properties. In patients with NASH, without diabetes, doses of 800 IU/day may improve liver inflammation and/or steatosis [Evidence level C]. Vitamin E has not consistently been shown to improve fibrosis. However, vitamin E is not without risk. It has been linked to hemorrhagic stroke (400 IU every other day), prostate cancer, all-cause mortality, and heart failure (400 IU/day). Potential adverse effects and benefits should be considered together prior to starting therapy. More data are needed before vitamin E should be considered for patients with mild NAFLD or coexisting type 2 diabetes. Milk thistle, also known as *Silybum marianum* or silymarin, has also been evaluated for its antioxidant properties as a treatment option for NASH. Small preliminary studies indicate milk thistle might improve liver enzymes and steatosis, especially when combined with vitamin E and phospholipids. Additional studies are needed to confirm these results. In addition, be aware that milk thistle might interact with medications through the cytochrome P450 system.

More...
**Conclusion**

For all patients with NAFLD, encourage lifestyle modifications including diet and exercise to achieve a minimum weight loss of 3% to 5% with a goal of at least 7% to 10%. In addition, recommend avoiding heavy alcohol consumption. Comorbid conditions should also be addressed. Continue to use metformin first-line to control blood sugar in patients with type 2 diabetes. Rely on statins first-line to manage high cholesterol. Control blood pressure with evidence-based therapies, taking comorbid conditions into account. For patients with NASH, weigh the risks and benefits of using pioglitazone in patients requiring additional glucose control or even in those without diabetes. Encourage vitamin E 800 IU daily in NASH patients without diabetes. Watch for more data on the impact of other medications (e.g., liraglutide, SGLT2 inhibitors) on NASH.

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

**Levels of Evidence**

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

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*Outcomes that matter to patients* (e.g., morbidity, mortality, symptom improvement, quality of life).  

**References**


11. Yee HF. The role of pioglitazone in the management of nonalcoholic steatohepatitis: are we there yet? *JAMA Intern Med* 2017;177:640-1.


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*Cite this document as follows: Clinical Resource, Overview of Nonalcoholic Fatty Liver Disease. Pharmacist’s Letter/Prescriber’s Letter. September 2017.*