Controversies in the Management of NAFLD

Mary E. Rinella, MD
Northwestern University Feinberg School of Medicine
Chicago, IL

Key Concepts

• NAFLD is recognized as the most common cause of chronic liver disease in the United States, and its frequency as a primary indication for liver transplantation is steadily increasing.
• While the diagnosis of NAFLD can be made through imaging studies or liver biopsy, the diagnosis of NASH still requires histological confirmation.
• Liver biopsy should be performed in the presence of risk factors for advanced disease, irrespective of the presence of aminotransferase elevation.
• Measures aimed at promoting weight loss, healthier lifestyle, and optimization of metabolic risk factors remains the cornerstone of management in NAFLD.
• Therapeutic agents presently considered the most promising in NAFLD are beneficial in less than 50% of patients. Therefore, future studies to identify additional therapies are a crucial need, as well as research to determine which patients are more likely to respond to current and future therapies.

Summary

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States. Non-alcoholic steatohepatitis (NASH), characterized by the presence of hepatocellular injury, is progressive in a substantial proportion of cases and can lead to cirrhosis and all its complications.

Liver ultrasound is routinely utilized for the diagnosis of NAFLD in clinical practice. It is widely available, convenient, safe, and the most affordable imaging technique for the assessment of hepatic steatosis. However, it lacks sensitivity and performs poorly when the steatosis is mild. Magnetic resonance imaging (MRI)-based methods including MRI-proton-density-fat-fraction, and MR spectroscopy (MRS) can accurately quantify liver fat content, and are emerging as the diagnostic test of choice in detecting longitudinal changes in liver fat content, and perform better than liver histology for assessment of hepatic steatosis. Despite recent advances in imaging modalities current methods remain unable to distinguish NASH from simple steatosis. In addition, non-invasive serological tests to diagnose NASH are neither sensitive nor specific enough yet to be used reliably in the clinical setting. Not all patients with NAFLD should undergo liver biopsy. Patients with higher likelihood of underlying NASH and advanced fibrosis would likely benefit most from liver biopsy. Optimization of metabolic co-morbidities is extremely important in the management of NASH. The number one cause of mortality in patients with NAFLD is cardiovascular, and therefore it is crucial to aggressively treat metabolic risk factors including diabetes, obesity, dyslipidemia, and hypertension in this patient population. Among patients with biopsy-proven NASH, treatment with
pharmacological agents should be considered; however, the role of specific agents in NASH still needs further study.

**Prevalence and Natural History – Why NAFLD Matters**

Nonalcoholic fatty liver disease (NAFLD) is characterized by the presence of excessive lipid accumulation in hepatocytes in the absence of significant alcohol consumption or other potential secondary causes. The reported prevalence of NAFLD varies significantly depending on the population being studied and on the diagnostic method used (1). The vast majority of patients with NAFLD have isolated hepatic steatosis. However, a proportion of NAFLD patients have NASH, with accompanying hepatocyte injury and inflammation.

It is estimated that approximately one-third of the US population has NAFLD. This estimate is based on a cross-sectional study of 2200 adults of various ethnicities in Dallas County, TX (2). The prevalence of NAFLD is higher among specific sub-populations with diagnostic elements of the metabolic syndrome. Studies of morbidly obese patients have demonstrated a prevalence of NAFLD of up to 90%, along with higher rates of NASH and advanced fibrosis (3). Similar higher prevalence of NAFLD and NASH has been described among patients with type 2 diabetes and those with dyslipidemia (4, 5).

Although NAFLD in the absence of hepatocellular injury has a lower risk of histological progression, NASH is progressive in a significant proportion of cases and can lead to cirrhosis and all its complications (6, 7). Furthermore, recent studies have suggested that the progression of nonalcoholic fatty liver, even in the absence of hepatocellular injury on biopsy, might be substantially higher than previously thought particularly when elements of the metabolic syndrome are present (8-10). Overall, the risk of death among patients with NAFLD is higher compared to that of the general population. The primary cause of death in patients with NAFLD is cardiovascular disease, followed by extra-hepatic malignancy, and liver disease (9).

**Non-Invasive Tests – Are We There Yet?**

Recently, concerns have been raised regarding the risk of NAFLD under-diagnosis due in great part to over-reliance on aminotransferases (11,12). In addition to suspecting NAFLD in patients with ultrasound findings compatible with fatty liver and in those with elevated aminotransferases, underlying NAFLD should be suspected in all patients with metabolic risk factors (12).

**Steatosis**

Liver ultrasound is the most common initial imaging technique for the diagnosis of NAFLD. Compared to other imaging studies it is widely available, convenient, safe, and relatively inexpensive. However, it has limited sensitivity when steatosis is less than 30%. Computed tomography also has limited sensitivity if steatosis is mild, is costly, and involves radiation exposure. Magnetic resonance imaging, including spectroscopy (MRS) has higher sensitivity and specificity in quantifying steatosis and is also safe, however it is expensive and in the case of MRS, not widely available (13).

**Hepatocellular Injury and Fibrosis**

The main limitation of imaging studies is in their inability to differentiate NASH from isolated hepatic steatosis. Noninvasive assessment of liver fibrosis is developing rapidly and is fairly reliable in distinguishing mild/no fibrosis from very advanced fibrosis but lacks sensitivity and specificity in the diagnosis of more moderate degrees of fibrosis. The best studied modality to detect fibrosis radiographically is transient elastography (TE, Fibroscan®). Results are promising however it is not widely available in the US. Other emerging techniques include another US based technique, acoustic radiation force impulse (ARFI) and MR elastography. ARFI has comparable AUROCs to TE for the detection of F >2 or cirrhosis in both non-transplant and transplant populations. (14)(Crespo J Hep 2012) MRE is not widely available, though an increasing amount of centers are using it. It has been shown in both retrospective and prospective data sets to be promising for the quantification of hepatic fibrosis in NAFLD.(15,16)(Godfrey European Radiology 2012; Kim et al Radiology 2013) In fact, prelim data suggest it may be able to distinguish NASH from simple steatosis.(17) (Chen Radiology 2011) Further studies are needed to address limitations of test performance related to high BMI, higher degrees of hepatic steatosis, narrow rib spaces, timing of last meal and acute hepatitis (18)(Berzigotti PLoS one, 2013).

Several individual parameters and combinations of clinical and laboratory parameters have been studied in an attempt to non-invasively diagnose NASH (19). Among these, cytokeratin 18 level has shown good correlation with the presence of NASH (19, 20), however it provides limited information compared to liver biopsy and lacks enough accuracy, thus its applicability outside of the clinical research setting is not yet elucidated. Future studies of cytokeratin 18, other markers, and combination of markers,
are needed including assessment of performance characteristics in different populations, longitudinal evaluation, and evaluation in the setting of interventional studies. The ability to predict advanced fibrosis in patients with NASH has also been extensively studied. Among these, the NAFLD fibrosis score (21) and the Enhanced Liver Fibrosis (ELF) panel (22) are examples of combinations of clinical and/or laboratory parameters that allow the prediction of severe fibrosis in NAFLD with good accuracy (23). Although non-invasive methods to predict advanced fibrosis in patients with NASH are not widely used in clinical practice, in the future, they may facilitate the identification of a majority of patients with severe fibrosis without the need for a liver biopsy.

**Controversy: Who to Biopsy?**

Liver biopsy remains the 'gold standard' for the diagnosis and staging of NASH. The presence of NASH on initial liver biopsy is the main predictor for the development and progression of liver fibrosis (6, 7). In turn, progression of liver fibrosis is the main determinant of adverse liver-related clinical outcomes. Therefore, diagnosing NASH and cirrhosis have crucial prognostic and management implications. However, liver biopsy is expensive, has associated risks, and has limitations.

Patients with persistent elevation in aminotransferases (>6 months) OR imaging consistent with NAFLD in the setting of metabolic co-morbidities should be considered for liver biopsy. It is important to note that often, as liver disease progresses due to NASH, aminotransferases may normalize. Any evidence on laboratory testing (AST:ALT>1, low platelets or evidence of synthetic dysfunction) or physical exam of advanced liver disease should prompt biopsy to exclude cirrhosis. Non-invasive prediction scores could be used to select patients with a higher likelihood of NASH and advanced fibrosis who should undergo liver biopsy (24-26). Patients with metabolic syndrome, or metabolic risk factors, particularly diabetes are at high risk of NASH and advanced fibrosis. Other important risk factors for advanced disease include those with a family history of diabetes, Hispanic or Asian ethnicity and the elderly. It is important to note that not all patients with NASH are obese (BMI>30). For example, Asian patients are at increased risk of metabolic disease (including NASH) at a lower BMI.

The NAFLD fibrosis score (21), is an example of a predictive score that can be calculated from routine data (age, body mass index, hyperglycemia, platelet count, albumin, and AST/ALT ratio) to help identify patients with more severe disease that would benefit most from liver biopsy (21, 240).

**Who Should be Treated and With Which Agent?**

The management of NAFLD involves attention to metabolic risk factors in addition to the liver. Given that the main cause of mortality in patients with NAFLD is cardiovascular, metabolic risk factors including diabetes, obesity, dyslipidemia, and hypertension should be optimally managed. Lifestyle modifications including weight loss and regular exercise are recommended. Weight loss of at least 5 - 9% of body weight resulting from lifestyle modifications appears to correlate with histological improvement in patients with NASH (27, 28). Exercise alone even without weight loss may have histological benefits as well (29, 30).

Several therapeutic agents have been studied in NAFLD. Pioglitazone (a thiazolidinedione) has been associated with histological improvement in NASH compared to placebo (31, 32). It is associated with several potential side effects such as heart failure, post-menopausal bone loss and small risk of bladder cancer (33). Weight gain is a common side effect (31, 34). While weight gain is in the form of less metabolically active adipose tissue, obese patients are often resistant to additional weight gain. Despite these potential side effects, pioglitazone is an option for the treatment of NASH, however perhaps best suited in those with impaired glucose tolerance or diabetes.

A recent study showed that therapy with Vitamin E (rrr-alpha tocopherol) at 800 IU per day in patients with NASH resulted in histological improvement in a greater number of patients compared to placebo (34). However, the study was limited to non-diabetic patients and therefore the conclusion cannot be extrapolated to patients with diabetes. In addition, there are concerns (albeit controversial) regarding the long-term safety of Vitamin E given reports that it may increase all-cause mortality (35, 36). Furthermore, treatment with vitamin E may be associated with an increased risk of developing prostate cancer as suggested by a recent trial of approximately 35,000 men (37). There are insufficient data to recommend vitamin E for NASH patients with concomitant diabetes or cirrhosis. Importantly, there is no evidence that Vitamin E improves fibrosis, which may be the most relevant histological endpoint. Based upon a meta-analysis of four randomized trials there is a suggestion that pioglitazone may improve fibrosis. However, further long term, and adequately powered studies are needed to assess the efficacy of these agents in assessing regression of fibrosis.

Interestingly, pentoxifylline has also been associated with histological improvement in smaller randomized trials.
of patients with NASH (38, 39), including improvement in fibrosis (39, 40). It appears that these beneficial effects are at least partly mediated through decreasing oxidative stress (41). However, future studies are needed to substantiate these results in larger groups of patients.

Although there is evidence of potential beneficial effect of some pharmacological agents, to date, there is no formally approved medical therapy for NASH. There is a major unmet need for therapeutic options for patients with NASH cirrhosis and for drugs that improve fibrosis. Ongoing and future trials will hopefully offer additional and more effective therapies for the growing numbers of patients with liver disease due to NASH.

References


