NAFLD Review: Diagnosis, Treatment and Outcomes

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of abnormal serum aminotransferase levels both in developed and developing countries. Patients with nonalcoholic steatohepatitis (NASH), a subset of NAFLD are at risk for progressive liver disease and in need of effective treatment options. A practical approach may be pursued by identifying patients with NAFLD with the highest likelihood for histologic evidence of NASH. Despite decades of clinical trials, no single treatment can be recommended to all patients with NASH. Importantly, there is no evidence that pioglitazone or vitamin E improves fibrosis. Bariatric surgeries may improve hepatic histology in morbidly obese patients with NASH, although randomized clinical trials are lacking. Currently, NASH is the second leading etiology of liver disease among adults awaiting liver transplantation (LT) in the U.S. The primary and secondary prevention of NAFLD may require aggressive strategies for managing obesity, diabetes and metabolic syndrome.
NAFLD: Definition and Classification

NAFLD is a clinical disease state characterized by the histological finding of 5% or greater macrovesicular steatosis of hepatocytes in an individual without significant alcohol use or other known causes of chronic liver disease (1). The histological spectrum of NAFLD extends from isolated steatosis or nonalcoholic fatty liver (NAFL) to NASH-related cirrhosis. While not entirely a diagnosis of exclusion, the diagnosis of NAFLD does require a careful query of alcohol consumption, as alcoholic liver disease itself can often demonstrate similar histological features to NAFLD. As such, current guidelines recommend utilizing criteria requiring alcohol exposure of less than 30 g/day for men and less than 20 g/day for women as a component of NAFLD diagnosis.

NAFLD: Incidence and Prevalence

NAFLD is the most common cause of elevated serum aminotransferase levels both in developed and developing countries (1-3). Globally, the prevalence of NAFLD is rising as a result of increasingly sedentary lifestyle, globalization of Western diet and improving food supplies in famine stricken areas of the past (4). While data are limited regarding the incidence trends of NAFLD, it would not be unexpected that rising incidence is observed given the trends in obesity and obesity-related diseases (1). However, both incidence and prevalence trends must be interpreted with caution, as improved understanding, awareness, and diagnosis of NAFLD may also be influenced by misclassification biases and selection biases. Furthermore, the prevalence estimates of NAFLD can vary
depending on the population studied and the accuracy of the diagnostic test (5).
Despite these limitations, it is currently estimated that the global prevalence of
NAFLD is as high as one billion (4). In the U.S., NAFLD is estimated to be the most
common cause of chronic liver disease, affecting between 80 and 100 million
individuals, among which nearly 25% have NASH. This form of NAFLD is
characterized by histologic evidence of progressive hepatocellular injury
(ballooning and inflammation) which can lead to cirrhosis and cirrhosis-related
complications such as hepatocellular carcinoma (HCC) and need for LT (1, 6, 7).
While previous studies have demonstrated the increasing rates of NASH-related
LT from 1.2% in 2001 to 9.7% in 2009 to become the third most common
indication for LT in the U.S., a recent study using registry data from the United
Network for Organ Sharing/Organ Procurement Transplant Network
(UNOS/OPTN) demonstrated that in 2013, NASH became the second leading
etiology of liver disease among adults awaiting LT in the U.S. and is predicted to
become the leading indication for LT in the near future (7, 8). In addition, NASH is
currently the second leading etiology and the most rapidly growing indication
among adults with HCC undergoing LT in the U.S. (9).

**NAFLD: Natural History and Predictors of Outcome**

The risk of NASH progressing to cirrhosis has not been clearly delineated, but
it has been estimated to range from 21% to 26% over 8.2 years (10). Up to 30% of
NASH patients with compensated cirrhosis develop hepatic decompensation in 8 to
10 years (11). While the development of cirrhosis among NAFLD patients increases
the risk of developing cirrhosis-related complications such as hepatocellular carcinoma and hepatic decompensation, earlier stages of fibrosis can also predict worse outcomes (12, 13). Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD. No other histologic features were associated with long-term outcomes of patients with NAFLD. Angulo et al performed a retrospective international longitudinal study of 619 NAFLD patients and demonstrated that increasing severity of liver fibrosis on biopsy was associated with increasingly higher risk of death, liver-related events, or liver transplantation (13). The risk of HCC is roughly 7% over 6.5 years (10, 11). The three major causes of NASH-related mortality, include cardiovascular disease (mortality range, 13% to 30%), all-cause malignancy (mortality range, 6% to 28%) and liver-related death (mortality range, 2.8% to 19%) (11). NAFLD and alcoholic liver disease may coexist in patients with metabolic syndrome with alcohol intake >60 g/day for men and >40 g/day for women, which may further contribute to a more aggressive natural history of illness (14). Individuals with a tendency for binge drinking have a higher risk for alcoholic steatohepatitis (14). Fortunately, most patients with NASH will outlive their liver disease and are more likely to develop fatal complications from cardiovascular disease. Therefore, the protective role of modest alcohol use to reduce morbidity and mortality associated with underlying cardiovascular disease needs further evaluation (15). Meta-analysis suggests that modest alcohol use may favorably impact the prevalence of NAFLD and progression to NASH (16). However, these data must be reproduced in a prospective fashion and remain controversial (16). On the
contrary, large prospective cohort studies have demonstrated that obesity and alcohol use can multiply the risk of liver-related death and HCC (17).

NAFLD is referred to as the hepatic manifestation of metabolic syndrome. Typically, most cases of metabolic syndrome-related NASH present with characteristic features of metabolic syndrome - central obesity, impaired glucose tolerance, high triglycerides, and low high-density lipoprotein [HDL] (18). In addition to high triglycerides and low HDL, patients with NAFLD are also noted to have higher low-density lipoprotein (LDL) particle concentration and lower LDL particle size (18). The abnormalities in lipoprotein profile in patients with NAFLD are suggestive of deranged lipid metabolism (19). While concurrent features of metabolic syndrome increase the risk of developing NAFLD, the presence of NAFLD also increases the risk of developing complications such as dyslipidemia and insulin resistance (20-22). The high prevalence of metabolic syndrome features observed among NAFLD patients emphasize the importance for evaluating for these risk factors so that early intervention can be implemented to improve long-term outcomes (20-22).

NAFLD: Diagnosis

The diagnosis of NAFLD incorporates the clinical history, laboratory data, radiographic data, as well as histologic information. NAFLD can be diagnosed non-invasively by the finding of hepatic steatosis on abdominal imaging study; liver biopsy is not always needed to confirm the diagnosis. However, a liver biopsy is required to distinguish isolated steatosis from NASH and to stage fibrosis severity,
which may subsequently affect risk of disease progression and disease management (23). Three key histologic features are needed to confirm the diagnosis of NASH (23, 24) and include steatosis, inflammation, and cellular ballooning (23).

**Diagnosis: Abdominal Imaging**

An abdomen ultrasound is operator dependent and lacks sensitivity in NAFLD patients with less than 30% steatosis on liver biopsy (25). However, ultrasound is noninvasive, without contrast-related risks, preferred by patients and widely available. Computed tomography (CT) is a radiation hazard, introduces contrast-related risks, has low sensitivity for hepatic fat mapping and is expensive (25). Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) provides the highest precision (sensitivity and specificity) in quantifying steatosis and liver fat mapping (26). Based on promising emerging data, MRI and MRS may become the gold standard for the diagnosis and management of NAFLD in the near future, although they are currently limited by cost and availability (27, 28). Currently, abdominal imaging studies are unable to accurately diagnose NASH. The role of transient elastography may be limited in subjects with high body mass indices (29). In patients with NAFLD, a hepatic stiffness measurement with MR elastography (MRE) is superior to MRI for the non-invasive diagnosis of significant liver fibrosis and cirrhosis (30). In addition, MRE may help identify individuals with steatohepatitis, even before the onset of significant fibrosis, although further studies are needed to validate this finding (31). NAFLD with inflammation but without
fibrosis demonstrates greater hepatic stiffness than isolated steatosis and lower mean stiffness than NAFLD with fibrosis (31).

**Diagnosis: Liver Biopsy**

Diagnosis of NASH requires a liver biopsy to confirm the characteristic histologic features. The considerable disease burden of NASH in the U.S. and the invasive nature of a liver biopsy have prompted experts to recommend its selective use in NAFLD patients with higher likelihood of progression to NASH. An individualized assessment is needed with discussion of risks and benefits of a diagnostic liver biopsy. Early diagnosis of NASH has crucial management implications and these patients may benefit from off-label therapy with promising agents (vitamin E and pioglitazone) or treatment in the setting of a therapeutic clinical trial (32-37). In the setting of advanced fibrosis or cirrhosis, steatosis may be absent (23, 32). Interobserver variability can occur during the histologic evaluation of hepatocellular ballooning on a liver biopsy sample among experienced pathologists (23, 24, 38, 39). The lack of agreement between pathologists regarding hepatocellular ballooning or sampling error may have resulted in a lower number of patients meeting the entry criteria in clinical trials (32). Therefore, a liver biopsy has several limitations as a diagnostic modality in patients with NASH. Patients who are noted to have isolated hepatic steatosis with any degree of necroinflammation on an index liver biopsy are at increased risk for progressive histologic damage, albeit at a lower rate than those with NASH (40, 41). In addition, patients with isolated hepatic steatosis and inflammation on liver
biopsy and with clinical diagnosis of metabolic syndrome or individual components of metabolic syndrome may be at risk for more rapidly progressive histologic damage (40, 41). Table 1 tabulates the predictors of histologic evidence of NASH on an index liver biopsy in patients with NAFLD. The indications for a liver biopsy in the setting of NAFLD includes patients with persistently elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels who have fatty liver on abdominal imaging study, age 65 years or older, metabolic syndrome or component(s) of metabolic syndrome, suspicion of other coexisting liver disease, and suspicion that another liver disease has been misdiagnosed as NAFLD (1, 10, 20, 42-45). However, the age and clinical indications for which liver biopsy is recommended vary based on the number and severity of baseline risk factors. Furthermore, while a major goal of liver biopsy is to stage severity of fibrosis, early diagnosis of NASH to distinguish from simple steatosis may also be important given the increased risk of disease progression and adverse outcomes associated with NASH, and the potential for initiating current and future therapies.

**Diagnosis: Noninvasive Biomarkers**

The limitations of liver biopsy, high prevalence of NAFLD and the lack of agreement on the clinical predictors of NASH have created a need to develop the next generation of noninvasive biomarkers to differentiate NAFLD from NASH (46). The potential role of numerous noninvasive clinical and laboratory markers has been studied to diagnose NASH in patients with NAFLD (46). Noninvasive markers of liver fibrosis can differentiate lack of fibrosis or mild fibrosis from advanced
bridging fibrosis or cirrhosis (46, 47). However, noninvasive tests lack the ability to reliably detect intermediate or moderate grade and stage of hepatic injury (46, 47). In addition, routine abdominal imaging studies lack the ability to diagnose NAFLD with less than 30% hepatocyte fat content (48). Keratin 8/18 immunostaining and other next generation noninvasive biomarkers may become available in the near future (49). Based on preliminary data, levels of cytokeratin 18 are associated with the presence of NASH, but lacks sensitivity and the histologic details provided by a liver biopsy (50, 51). Several panels have been developed and studied to predict the presence of advanced fibrosis in patients with NASH (52). The NAFLD fibrosis score (53) and FIB-4 are derived from readily available clinical markers for the assessment of advanced fibrosis (54). The Enhanced Liver Fibrosis panel utilizes an extracellular matrix marker panel to predict the stage of fibrosis in patients with chronic liver disease (55). While liver biopsy currently offers the most accurate assessment of liver histological stage and grade of disease, the emerging availability of non-invasive biomarkers holds promise in providing an alternative to biopsy. The goals of non-invasive biomarkers are to predict the risk of developing disease progression, including NASH and severity of fibrosis, thereby providing risk stratification for development of poor clinical outcomes such as cirrhosis, hepatocellular carcinoma, or hepatic decompensation.

**NAFLD: Treatment and Outcomes**

Many controversies have persisted with respect to treatment of NAFLD (1). Chief among these is the inherent limitations in our ability to accurately
distinguish different stages of NAFLD, as targeted therapy for NAFLD requires precise categorization of NAFLD into NAFL or NASH. A proactive treatment approach is prudent in patients with biopsy-proven NASH due to the risk of progressive histologic damage. Several promising pharmacologic agents need to be further studied in patients with NASH (1, 56-58). The most fundamental step in the management of NAFLD is treating the risk factors that are commonly associated with metabolic syndrome through lifestyle modifications, which may serve as both primary and secondary prevention for NAFLD (57, 59, 60).

**Treatment and Outcomes: Exercise Program**

The adverse consequences of obesity, diabetes mellitus and other components metabolic syndrome in patients with NAFLD are further compounded by the lower level of physical activity and lack of aerobic exercise noted in this patient population (61). It appears that exercise alone, independent of weight loss, may result in histologic improvement in these patients (62). It is suggested that 120 minutes of aerobic exercises, such as running and swimming every week increases glucose uptake by improving insulin sensitivity (63). Exercise stimulates protein synthesis and improves muscle mass, while sedentary lifestyle leads to muscle breakdown (59). Incremental rise in fat-free, lean mass induced by aerobic exercise results in efficient glucose uptake with reduction in hepatic fat content and provides protection against NAFLD. A systematic review which analyzed data from randomized controlled trials noted that exercise can reduce hepatic fat content without affecting ALT (64). An individualized exercise
regimen needs to be developed based on the severity of underlying hepatic
dysfunction from NAFLD, class of obesity, exercise tolerance status, presence of
individual components of metabolic syndrome and other comorbid medical
problems in a given individual.

_Treatment and Outcomes: Dietary Modifications_

It is important to establish a detailed dietary plan to effectively manage the
daily caloric intake in conjunction with exercise to induce weight loss without
malnutrition. Based on observations from small studies, a weight loss of 7% or more
with intense dietary counseling over one year may improve histology in patients
with biopsy-proven NASH (65, 66). Most guidelines regarding hypocaloric diet
suggest 1000-1200 calories per day for women and 1200-1600 calories per day for
men with a goal to achieve a weight loss of 0.5 to 1.0 kg per week (67).
Macronutrients including carbohydrate, protein, fat and micronutrients including
vitamins, minerals, and supplements must be balanced. It has been demonstrated
that more durable weight loss can be achieved in patients with NAFLD by combining
diet and exercise for longer than 12 months (68). Data on the role of certain
nutritional supplements to improve exercise performance are encouraging. Caffeine
improves performance and may be protective against the development of NAFLD
(69). Data from the National Health and Nutrition Examination Survey showed that
two cups of caffeinated coffee per day associated with a lower risk for NAFLD
suggesting a potential protective effect (69). Consumption of caffeinated coffee is
associated with a significant risk reduction of fibrosis in the setting of NASH (70).
**Treatment and Outcomes: Pharmacotherapy**

In addition to weight reduction strategies to address obesity-related NAFLD, a number of medical therapies have been studied in patients with NASH. These include antioxidants, such as vitamin E; insulin sensitizers, such as pioglitazone and metformin; lipid-lowering agents, such as statins; and cytoprotective agents, such as ursodeoxycholic acid (1, 32, 35). Despite decades of clinical trials, current evidence suggests that only vitamin E may be beneficial for treatment of nondiabetic patients with NASH, but no single treatment can be recommended to all patients with NASH (1, 32). Thiazolidinediones (TZDs) are selective peroxisome proliferator-activated receptor-gamma agonists with clinical evidence of therapeutic benefit (71-74). TZDs improve insulin sensitivity of adipose tissue, liver and muscle (71, 72). Pioglitazone demonstrated hepatic histologic benefit in clinical trials by improving steatosis, lobular inflammation, and ballooning degeneration (73, 74). Subsequently, in a clinical trial 247 nondiabetics with histologic evidence of NASH were randomized to one of 3 groups to receive pioglitazone 30 mg, vitamin E 800 IU, or placebo for 96 weeks (32). The primary endpoint was evaluated by NAFLD Activity Score and required histologic improvement in NASH including hepatocyte ballooning. While the primary endpoint was not met in the pioglitazone group, faulty randomization of balloon degeneration in the pioglitazone group compared to the other two groups may have limited the study’s ability to detect a significant benefit. It is important to recognize that 47% of the subjects receiving pioglitazone demonstrated
complete resolution of steatohepatitis at end-of-treatment biopsy versus 21% in the placebo group (P=0.001). In summary, the clinical trial provided evidence that optimization of insulin sensitivity is pivotal in the management of NASH. Two meta-analyses of randomized controlled trials showed that pioglitazone was able to promote regression of hepatic fibrosis in patients with NASH (75, 76). In addition, pioglitazone may reduce mortality related to ischemic cardiovascular events, which is the most common cause of death in patients with NASH (77). However, pioglitazone has a Food and Drug Administration black box warning in the U.S. that it may precipitate congestive heart failure in at-risk individuals, without any increase in cardiovascular or all-cause mortality. Overall, pioglitazone has a favorable safety profile and is an effective option for the treatment of insulin-resistant patients with type 2 diabetes with or without NASH. While optimizing management of insulin resistance among NAFLD patients is important, the role of metformin in the treatment of NASH patients is less clear. Several studies evaluating the effect of metformin on disease progression among NASH patients have provided conflicting results (36, 78, 79). A recent meta-analysis by Veron et al demonstrated no significant benefit of metformin in improving serum aminotransferases or liver histology among NAFLD patients with or without diabetes (80).

Vitamin E supplementation with 800 IU/day studied in a large, double-blind, randomized, placebo-controlled trial demonstrated superiority versus placebo by improving ALT levels and NASH-related histologic damage (32). The improvement in NASH-related inflammation and fibrosis noted with vitamin E therapy was most
likely induced by suppression of lipid peroxidation and oxidative stress (81). In a
meta-analysis, vitamin E supplementation increased all-cause mortality, possibly
related to unfavorable changes in plasma lipoproteins (82). Although these data
have been challenged, it is important to keep in mind that therapy with high-dose
vitamin E may not be without adverse effects (83, 84). The available evidence
suggests that vitamin E improves liver enzymes, steatosis, and liver injury in NASH
patients without diabetes. There are insufficient data to recommend vitamin E for
patients with NASH and concomitant diabetes or cirrhosis. Importantly, there are no
prospective data demonstrating that pioglitazone or vitamin E improves fibrosis,
which may be the most relevant histologic endpoint.

Bile acid derivative 6-ethylchenodeoxycholic acid (obeticholic acid) is a
potent activator of the farnesoid X nuclear receptor that reduces liver fat and
fibrosis in animal models of fatty liver disease (35). Obeticholic acid improved the
histological features of NASH, but its long-term benefits and safety need further
clarification (35). A recently published study by the NASH clinical research network,
the FLINT trial, reported findings of a multicenter, double-blind, placebo-controlled
randomized clinical trial evaluating the effect of obeticholic acid treatment among
non-cirrhotic patients with NASH. Among patients treated with obeticholic acid,
45% achieved improved liver histology (defined as a decrease in NAFLD activity
score by at least 2 points without worsening of fibrosis from baseline to the end of
treatment) compared with 21% among the placebo group (RR, 1.9; 95% CI, 1.3-2.8).
While more studies are needed to confirm the potential beneficial effect of
obeticholic acid, the FLINT trial provides promising outcomes (35). Another
potential therapy in phase 2 clinical trials is simtuzumab, an antifibrotic monoclonal
antibody that targets the lysis oxidase-like 2 (LOXL2) enzyme. Data from these trials
in both stage 3 and 4 NASH patients are eagerly anticipated. Pentoxifylline is
another agent that has shown promise in smaller pilot trials (85). It appears that
these beneficial effects are at least partly mediated through decreasing oxidative
stress (85). However, future studies in larger groups of patients are needed to
substantiate these results.

**Treatment and Outcomes: Surgical Options**

Despite the high prevalence of NAFL and NASH among morbidly obese
surgical patients, this condition was not associated with increased risk for
postoperative complications following bariatric surgery (86). In the setting of
cirrhosis, bariatric surgery is only indicated in patients with compensated cirrhosis
and contraindicated for patients with hepatic decompensation (87). Bariatric
surgery is associated with the most rapid, sizable and durable weight loss, and
ranges from 20% to 40% (88). Approximately 75% of weight loss is sustained for at
least a decade or longer following bariatric surgery (89). The most commonly used
laparoscopic bariatric surgeries include Roux-en-Y gastric bypass (RYGB), vertical
sleeve gastrectomy (VSG), and adjustable gastric band (AGB). The routine use of
laparoscopic approach has resulted in lower postoperative complication rates
related to surgical wound and perioperative mortality (88). It is recommended that
patients be monitored for deficiencies in iron, vitamin B12, calcium, and vitamin D
(90). Due to the profound weight loss associated with bariatric procedures, the
impact on outcomes is significant (91). Patients with NAFL and NASH demonstrate histologic improvement with reduction in mortality from NASH-related complications following bariatric surgery (92). An impressive reduction in all-cause mortality of 30% to 40% has been reported within the 7 to 10 years following the bariatric procedure with the largest improvement in survival from diabetes, cardiovascular disease, and obesity-related malignancies (91). LT can be pursued in patients with hepatic decompensation in the setting of cirrhosis. Combined LT plus sleeve gastrectomy (SG) for obese patients who failed to lose weight prior to LT have been reported (93). In a single center study with small sample size patients undergoing the combined LT and SG, there were no deaths or graft losses, none of the patients developed diabetes or steatosis following LT, and all showed significant weight loss (93). These data were limited by a small sample size and lack of long-term follow up.

**Conclusion**

With the rising rates of obesity and obesity-related diseases, the worldwide prevalence of NAFLD has also demonstrated similar trends. While the importance of awareness can lead to early diagnosis of NAFLD, few pharmacological treatment options are currently available. Clearly, lifestyle and dietary programs can provide significant benefit, these strategies are not successful in all, and may not prove effective in patients with advanced stage or decompensated disease. Although there is evidence supporting a beneficial effect of some pharmacologic agents, to date, there is no formally approved medical therapy for NASH, and the magnitude of these
improvements is small. Ongoing and future trials will hopefully offer additional and more effective therapies for the growing number of patients with chronic liver disease due to NASH. A major limitation of the current data is that only a fraction of patients respond to therapy, and no agent has been convincingly shown to decrease fibrosis, arguably the most relevant therapeutic endpoint. Furthermore, trials exploring the potential additive effects of insulin sensitizers with cytoprotective agents or other modalities are eagerly awaited. As a result, there is a major unmet need for therapeutic options for the growing number of patients with NASH-associated cirrhosis. Management of NASH (Figure 1), like that of other complex metabolic diseases, will necessitate a multidisciplinary approach.
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Figure Legend

Figure 1: Management Algorithm for Patients with NAFLD: This diagram outlines the workup for a patient that presents with either elevated serum aminotransferases or fatty liver on imaging.
Elevated aminotransferases → Exclude alcoholic liver disease (ALD) → Rule out other causes of CLD → Risk factors for NASH (Table 1) → Fatty liver on abdominal imaging

No evidence of other CLD → No stigmata of cirrhosis → No risk factors for NASH (Table 1) → Lifestyle modifications → Repeat laboratory tests in 6 months

Lifestyle modifications → Resolution of abnormalities → Monitor every 6 months

Persistent abnormalities → Emergence of NASH risk(s) → Liver biopsy

Liver biopsy → NASH → Non-cirrhotic and CC: Consider RCT/bariatric surgery → Hepatoma surveillance in CC

Cirrhosis with HD: Hepatoma surveillance → Liver transplantation

NASH → Weight loss: lifestyle changes → Avoid alcohol and tobacco → DM: pioglitazone/metformin → Non-DM: vitamin E

NAFLD → Weight loss: lifestyle changes → Avoid alcohol and tobacco → Avoid metabolic syndrome → Primary prevention of CVD

ALD, alcoholic liver disease; CLD, chronic liver disease; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver or simple steatosis; DM, diabetes mellitus; CVD, cardiovascular disease; CC, compensated cirrhosis; RCT, randomized controlled trial; HD, hepatic decompensation in the setting of cirrhosis.