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The Natural History of Nonalcoholic Fatty Liver Disease - An Evolving View

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Introduction

Since being first described in 1980 (1), Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of hepatic fat, as evidenced by radiologic or histologic examination, in the absence of a coexisting etiology of chronic liver disease or secondary cause of steatosis (including drugs, significant alcohol consumption, or inherited or acquired metabolic states). The spectrum of NAFLD encompasses two subtypes: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Isolated NAFL is characterized by steatosis (may be associated with mild chronic inflammation) in at least 5% of hepatocytes.

On the other end of the spectrum, NASH is defined by a pattern of characteristics that include steatosis, lobular and portal inflammation, and liver cell injury in the form of hepatocyte ballooning. Lobular inflammation is classically mild, characterized by a mixed inflammatory cell infiltrate. Other potential histological findings include Mallory–Denk bodies, iron deposition, periportal hepatocytes with vacuolated nuclei, ductular reaction, megamitochondria, lobular lipogranulomas, periodic acid-Schiff–diastase–resistant Kupffer cells, and acinar zone 3 perisinusoidal/pericellular fibrosis, which may be indistinguishable from alcoholic steatohepatitis (2,3). In recent years, the NAFLD activity score (NAS), developed by The Pathology Committee of the NASH Clinical Research Network, has gained wide acceptance for histologically diagnosing NASH (4). The NAS assess the degree

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of steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis. However, the NAS does not supplant the pathologist's overall histologic evaluation (5).

Histologically, it is important clinically to establish the distinction between NAFL and NASH, as most NAFLD patients have steatosis without necroinflammation or fibrosis and do not require medical therapy. In its more advanced stages, NAFLD can progress to fibrosis, cirrhosis, and end-stage liver diseases with related complications, including hepatocellular carcinoma (HCC) (6).

In order to understand the clinical relevance of NAFLD, to define long-term outcomes, and risk-stratify patients for disease-related complications and mortality, it is important to understand the natural history of the disease. Long-term observational studies, paired liver biopsy studies, and high-quality global meta-analysis have better defined the course of NAFLD. However, conflicting data among studies persists, with resultant persistent ambiguity in the field. This review attempts to add to the current literature by summarizing recent high-quality evidence supporting the elucidation of the natural history of NAFLD.

Epidemiology

A recent systematic review and meta-analysis has estimated the global prevalence of NAFLD, as diagnosed by imaging in the absence of significant alcohol use, to be approximately 25%, with the highest prevalence in the Middle East and South America and the lowest prevalence in Africa. Metabolic comorbidities associated with a diagnosis NAFLD included obesity (51.34%), type 2 diabetes (22.51%), hyperlipidemia (69.16%), hypertension (39.34%), and the metabolic syndrome (42.54%) (7). In the United States, data from the National Health and Nutrition Examination Surveys conducted between 1988 and 2008 estimates that the prevalence of NAFLD increased from 5.5 to 11%, with concurrent increased prevalence of obesity, type II diabetes, insulin resistance, and hypertension. By contrast, the prevalence of Hepatitis B-, Hepatitis C- and alcohol-related chronic liver disease remained stable over the same period of time. NAFLD is increasingly being diagnosed in the pediatric population, with studies estimating prevalence rates of 3–18% (8–11).

Based on data collected from the United Network for Organ Sharing and Organ Procurement and the Transplantation Network registry from 2004 through 2013, NAFLD is now the most common form of chronic liver disease in the United States and is the second-most common indication for liver transplantation (12). The same study identified that new liver transplant waitlist registrants with NASH increased by 170%; however, these same patients experienced higher 90-day waitlist mortality and were less likely to undergo liver transplantation. NAFLD is on track to be the most common indication for liver transplantation by the year 2020 (13).

Clinical Significance of NAFLD

NAFLD is thought to be the hepatic manifestation of the metabolic syndrome, defined as the presence of 3 or more of the following: (1) abdominal obesity (waist circumference >102 cm in men, >88 cm in women), (2) hypertriglyceridemia (>150 mg/dL), (3) low high-density

lipoprotein (HDL) levels (<40 mg/dL in men, <50 mg/dL in women), (4) hypertension (>130/80 mm/Hg), and (5) high fasting glucose levels (>110 mg/dL) (14,15). The prevalence of NAFLD in patients with the metabolic syndrome (16), and particularly diabetes, is high (17,18). The global prevalence of obesity among NAFLD patients and among NASH patients is estimated to be 51% and 82%, respectively (7). In studies of patients with cryptogenic cirrhosis, greater than 60% of patients have been shown to have metabolic risk factors for NAFLD (19,20). NAFLD has also been associated with hypothyroidism (21), polycystic ovarian syndrome (22) and colonic adenomas and neoplasms (23).

Cardiovascular Disease

Metabolic syndrome is a powerful risk factor for cardiovascular disease, and multiple studies have demonstrated that cardiovascular disease is the leading cause of death in NAFLD patients, with NASH, fibrosis stage, and diabetes being the strongest risk factors for overall and liver-specific mortality (24–30). An early population study from Olmstead County (27) of 420 patients with NAFLD with a mean follow-up of 7.6 years, observed that patients with NAFLD have a higher all-cause mortality rate than age and sex- matched patients without NAFLD (standardized mortality ratio, 1.34; 95% CI, 1.003–1.76; P = .03) (27). The three-leading causes of death in patients with NAFLD were malignancy, ischemic heart disease, and liver disease, with higher mortality rates observed in older patients, and patients with impaired fasting glucose and cirrhosis.

A population-based study from the third National Health and Nutrition Examination Survey (NHANES III) (30) of 12,822 patients between 1988–1994, 80 patients with NAFLD (defined by elevated serum aminotransferases in the absence of other chronic liver disease) died, consistent with higher overall (HR 1.038; 95 % CI 1.036–1.041; p<0.0001) and liver-related mortality (HR 9.32; 95 % CI 9.21–9.43; p< 0.0001) than patients without NAFLD. Cardiovascular events were the leading cause of death in patients with suspected NAFLD, followed by non-hepatic malignancy and liver-related death.

In a follow-up study of NHANES III, suspected NAFLD (based on similar inclusion criteria), especially in the 45–54-yr-old age group, was demonstrated to be an independent risk factor for cardiovascular event-related death, though the elevated hazard ratio of 1.37 (95% CI 0.98–1.91) for all-cause mortality was found to be of borderline statistical significance (31).

A recent meta-analysis and systematic review of 16 observational or retrospective studies of patients with suspected NAFLD (based either radiological imaging or histology) found that patients with NAFLD were at higher risk of fatal and non-fatal cardiovascular events than those without NAFLD (random effect odds ratio [OR] 1.64, 95% CI 1.26–2.13)(32). In addition, patients with “severe” NAFLD, ie NASH with or without fibrosis, were also at elevated risk for fatal and non-fatal cardiovascular events (OR 2.58; 1.78–3.75). Patients with NAFLD also have higher rates of cardiovascular disease than patients with HCV. In a long-term follow-up study comparing the natural history of cirrhosis in patients with NASH to patients with HCV, patients with NASH had a significantly higher risk of cardiovascular-related mortality than their matched controls with HCV (8/152 vs. 1/150; P < .03) (33). The observational nature of these studies included in this systematic review falls short of

establishing causality with respect to cardiovascular disease, but prompts the need for intensified guidelines regarding cardiovascular screening strategies in patients with NAFLD.

Liver-Related Morbidity

In terms of histologic progression, dogma endures that NAFL carries a more favorable prognosis than NASH, which can histologically progress to fibrosis and, in up to 25% of patients, to cirrhosis (34,35). The evolution of fibrosis carries secondary risks, including complications associated with portal hypertension (ascites, variceal hemorrhage, hepatic encephalopathy), end-stage liver disease, and HCC. Liver-related death is the third-leading cause of death in patients with NAFLD (27,28). In developed Western nations, between 4 and 22% of cases of HCC are now attributed to NAFLD (36). Lack of awareness about risk factors for NAFLD and its progression, combined with insufficient or unreliable screening and surveillance modalities may contribute to a delay in diagnosis and may explain why many patients present in the later stages of the disease (37). The burden of NAFLD is associated with worldwide increased healthcare costs and resource utilization, as well as with decreased health-related quality of life (38).

Risk Factors for Progression

Steatosis

Hepatic steatosis occurs in the setting of insulin resistance and the metabolic syndrome modulated by visceral adipose tissue. This alteration of lipid and glucose metabolism can result in dysregulation of hepatic transcription factors and nuclear receptors, resulting in hepatic fat accumulation. Hepatic steatosis can create a proinflammatory environment, leading to cellular injury and necroinflammation (39,40).

In keeping with the hypothesis that NAFLD is the hepatic manifestation of the metabolic syndrome, weight gain has been associated with the development of NAFLD, and conversely, weight loss has been associated with regression of hepatic steatosis. In a sub-sample prospective ultrasound study of the first Israeli national health and nutrition examination survey (the MABAT Survey), 19% of patients who did not have imaging evidence of NAFLD at baseline were found to have NAFLD at a 7-year follow-up. Weight gain (5.8±6.1 vs. 1.4±5.5kg) was significantly higher in patients who developed NAFLD, compared with those did not. Of the patients who were found to have NAFLD at baseline, 36.4% had no imaging evidence of NAFLD after 7 years, associated with weight loss of 2.7±5.0kg, or a 5% decrease from baseline weight (41).

Pooled data from a recent global meta-analysis estimated the incidence rate for NAFLD in Asia and Israel were 52.34 per 1,000 (95% CI: 28.31–96.77) and 28.01 per 1,000 person-years (95% CI: 19.34–40.57), respectively (7). Whereas early studies suggested that simple steatosis was a benign condition that followed an indolent course (42), recent histologic paired liver biopsy studies of patients with baseline NAFL suggest that NAFL is more progressive than originally thought (43). In a prospective longitudinal study of 52 patients who underwent liver biopsy, 13 patients had simple steatosis at baseline. On follow-up biopsy at 26 months, 39% developed borderline NASH and 23% developed NASH. Weight

loss (specifically, reduced BMI and waist circumference) was independently associated with disease stability and non-progression to fibrosis (44). In a study of 108 patients with NAFLD over a median interval of 6.6 years, 27 patients had NAFL (steatosis alone or associated with mild inflammation). Of the patients with NAFL at baseline, 44% of patients developed NASH, 27% of patients developed fibrosis, and 22% of patients had bridging fibrosis on follow-up liver biopsy. A similar proportion of patients with NAFL at baseline had progressive fibrosis as patients with NASH on index biopsy (45). In a similar study of patients who underwent paired liver biopsies with a mean follow-up of 3.7 years, among 25 patients with NAFL, 64% progressed to NASH and 24% developed bridging fibrosis (46). In a 2015 meta-analysis of paired liver biopsy studies, Singh et al found that patients with NAFL and stage 0 fibrosis at baseline progressed 1 stage of fibrosis over 14.3 years. By comparison, patients with NASH and stage 0 fibrosis at baseline demonstrated an accelerated rate of progression, advancing 1 stage of fibrosis over 7.1 years (47).

Steatohepatitis and Evolution of Fibrosis

In comparison to isolated hepatic steatosis, the evolution of NASH and the associated risk factors for progression have been widely investigated. In a recent meta-analysis of patients with NAFLD who underwent liver biopsy, the global prevalence of NASH in NAFLD patients has been estimated to be 59% (7). Male sex, age, weight, total cholesterol, insulin resistance, hypertension, metabolic syndrome, thyroid stimulating hormone levels, vitamin D levels, hyperuricemia, and certain genetic polymorphisms are predictors of histologic findings diagnostic of NASH (48–55). Further, factors associated with progression of fibrosis in patients with NASH include age, inflammation at index biopsy, hypertension, and low AST to ALT ratio (47,56).

Argo, et al conducted a systematic review of ten studies inclusive of 221 patients in 2009, finding that 37.6% of patients with NASH had progressive fibrosis over a mean follow-up interval of 5.3 years (56). A recent meta-analysis analysis of 4 studies of patients with biopsy-proven NASH estimated a pooled mean fibrosis progression rate 0.09 (95% CI: 0.06–0.12); meta-analysis of 6 studies of patients with histological NASH estimated a percent fibrosis progression of 40.76% (95% CI: 34.69–47.13). However, quite alarmingly, 1 of every 5 patients who experienced progression were identified as being “rapid progressors” - patients who progressed from stage 0 fibrosis on initial biopsy to bridging fibrosis or cirrhosis at follow-up (7). Unfortunately due to the nature of the analysis, factors associated with rapid progression could not be distinguished, which identifies an important gap in our understanding of the natural history of NAFLD and related fibrosis, and calls for further investigation.

The presence and stage of fibrosis appear to be the most important predictors of cardiovascular and liver-related complications. In a long-term study of 229 patients with NAFLD, Ekstedt et al discerned that patients with fibrosis stage 3–4, irrespective of the histologic NAS, had increased mortality (HR 3.3, CI 2.27–4.76, $p < 0.001$), compared to a reference population from the National Registry of Population (24). This data is supported by a retrospective analysis of 619 patients with NAFLD from 1975 through 2005 at medical centers in the United States, Europe, and Thailand (57). Angulo et al observed that the

presence of fibrosis, independent of steatohepatitis, was associated with the need for liver transplantation, liver-related complications, and overall mortality. (57)

Advanced Fibrosis and Cirrhosis

Overall, we have more limited information on long-term outcomes and the natural history of advanced fibrosis and cirrhosis due to NAFLD. The global incidence of advanced fibrosis in NASH patients has been estimated in meta-analysis to be 67.95 in 1,000 person-years, with 41% of NASH patients experiencing fibrosis progression (average annual progression rate of 0.09%) (7). Up to 25% of patients with NAFLD progress to cirrhosis (35,58), and 7% to end-stage liver disease (34). Advanced fibrosis and cirrhosis secondary to NAFLD have also been observed in the pediatric population, in up to 8% of patients with histologic NASH (59). Obesity, diabetes, and carotid artery disease are predictive of advanced fibrosis and cirrhosis in patients with NASH (60–62). In addition, a systematic review of 10 studies encompassing 221 patients with NASH identified age and inflammation on initial liver biopsy as independent factors associated with progression to advanced fibrosis (56). In an early longitudinal study of 42 patients with NAFLD, Powell et al (63) observed that fibrosis progression to cirrhosis was associated with loss of steatosis and inflammation histologically.

Patients with NAFLD-related cirrhosis appear to have lower rates of liver-related morbidity and mortality than patients with HCV-related cirrhosis. In a prospective, international study of 247 patients with histologically proven NAFLD-related advanced fibrosis (grade 3) or cirrhosis, patients with NAFLD had lower rates of liver-related complications than age- and sex-matched patients with HCV-related advanced fibrosis or cirrhosis, including HCC. Rates of cardiovascular events and overall mortality were similar between the 2 groups (64). In a prospective study of 152 patients with NASH-related cirrhosis compared to 150 matched patients with HCV-related cirrhosis, at a 10-year follow-up, patients with Child Class A cirrhosis secondary to NASH had a significantly lower mortality than patients with similar patients with HCV (3/74 vs. 15/75; $p<0.004$), as well as a lower risk of decompensation ($p<0.007$). Similar mortality rates were observed in patients with Child Class B or C cirrhosis across groups. Patients with NASH had lower rates of ascites development, hyperbilirubinemia and HCC than comparable HCV patients(33). An earlier, similar study from Hui et al observed similar liver-related complication and overall mortality rates between patients with NASH-related cirrhosis and HCV-related cirrhosis, but also observed a lower rate of HCC in patients with NASH-related cirrhosis (65).

Powell’s early findings (63) can support re-classifying a large proportion of patients originally labeled as having cryptogenic cirrhosis as “burned-out NASH.” A large proportion of these patients have risk known factors for the metabolic syndrome (19,20), and histologically, though they may lack recognized features of NASH, these findings may have regressed concurrently with fibrosis progression (19,66). This is supported by the high prevalence of NASH in liver transplant recipients who were transplanted for cryptogenic cirrhosis (67).

Hepatocellular Carcinoma

Compared to alternative etiologies of chronic liver disease (for example, viral hepatitis, autoimmune or metabolic liver disease) that contribute to the global burden of HCC, patients with HCC attributed to NAFLD tend to be older and female. The development of HCC in NAFLD patients has been associated with age, obesity, diabetes, the PNPLA3 I148M polymorphism, dietary habits and drugs (66,68). The annual incidence of HCC in NAFLD patients has been estimated to be 0.44 per 1,000 person-years in a global meta-analysis. By comparison, the annual HCC incident rate in patients with NASH was 5.29 per 1,000 person-years (7). A recent Surveillance, Epidemiology and End Results (SEER) database study demonstrated a 9% annual increase (over a 6-year period, 2004–2009) in the number of HCC cases attributed to NAFLD. The authors also observed that patients with NAFLD and HCC had a shorter survival time after diagnosis, more cardiovascular events, and were more likely to experience liver cancer-related mortality than patients without NAFLD (69). Finally, and distressingly, HCC in patients with metabolic syndrome and NAFLD has been observed in the absence of significant fibrosis or cirrhosis (70,71). As a result, HCC is frequently diagnosed at a more advanced stage than in patients with viral hepatitis, possibly the consequence of insufficient surveillance, which may contribute to the poorer prognosis observed in several studies (72).

Recurrence after Liver Transplantation

Recurrence of NAFLD and NASH has been reported in patients who have received liver transplantation, associated with persistence of the metabolic syndrome post-LT, and negatively associated with weight loss after LT (73–75). In an early series of 622 liver transplant recipients (73), 8 female patients had histologic features of NAFLD pre-LT. At a median follow-up of 15 months, 6 patients developed steatosis, 3 of whom had features consistent with NASH, and 2 patients progressed from mild steatosis to NASH within 2 years of LT. In a case-control single-center study of patients undergoing LT from 1997 to 2008 (74), 98 patients were transplanted for NASH. Recurrent NAFLD, NASH and advanced fibrosis were seen in 70%, 25% and 18%, respectively, of patients at a mean follow-up of 18 months. Patients with recurrent NASH did not develop graft failure or require re-transplantation at a mean follow-up of 3 years. In a study comparing post-LT outcomes between patients transplanted for NASH and patients transplanted for alcoholic liver disease (75), steatohepatitis post-LT was more common in patients transplanted for NASH (33 v. 0%), but there was no statistically significant difference in rates of graft failure or re-transplantation, or in post-LT survival.

Conclusions

NAFLD is a burgeoning epidemic in the United States and worldwide, and its clinical and economic impact will continue to grow with parallel increases in rates of obesity, diabetes, and the metabolic syndrome. Our evolving understanding of the natural history of NAFLD suggests that patients with steatosis may be at a higher risk for disease progression to steatohepatitis and subsequently to fibrosis and cirrhosis than previously thought. Recent studies also suggest that these patients are at elevated risk for cardiovascular-, malignancy-

and liver-related morbidity and mortality, though their risk for progression, decompensation and development of HCC may be less than that of patients with HCV. Continued study of the natural history of NAFLD and its complications through the conduction of high-quality, prospectively designed studies is needed. An improved understanding of the natural history of NAFLD, with definition of factors associated with progression and long-term outcomes, will lend itself to the development of enhanced prevention, screening, surveillance, and treatment modalities.

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KEY POINTS

- Nonalcoholic fatty liver disease (NAFLD) is a worldwide epidemic, with global prevalence increasing in parallel with rates of obesity, diabetes and the metabolic syndrome.
- Our understanding of the natural history of NAFLD is evolving; recent studies suggest that both patients with steatosis and steatohepatitis are at risk for progression.
- Patients with NAFLD experience elevated rates of cardiovascular events and higher-than-expected all-cause mortality; fibrosis is the strongest predictor of liver-related complications and mortality.

SYNOPSIS

NAFLD is a major etiology of chronic liver disease worldwide, and its clinical and economic burden will continue to grow with parallel increases in rates of obesity, diabetes, and the metabolic syndrome. Our evolving understanding of the natural history of NAFLD suggests that these patients are at risk for disease progression to steatohepatitis, fibrosis and cirrhosis. Recent studies also suggest that these patients are at elevated risk for cardiovascular-, malignancy- and liver-related morbidity and mortality, though their risk for progression, decompensation and HCC may be less than that of patients with alternative etiologies of chronic liver disease.