NASH is an Inflammatory Disorder: Pathogenic, Prognostic and Therapeutic Implications

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While non-alcoholic fatty liver disease (NAFLD) is highly prevalent (15% to 45%) in modern societies, only 10% to 25% of cases develop hepatic fibrosis leading to cirrhosis, end-stage liver disease or hepatocellular carcinoma. Apart from pre-existing fibrosis, the strongest predictor of fibrotic progression in NAFLD is steatohepatitis or non-alcoholic steatohepatitis (NASH). The critical features other than steatosis are hepatocellular degeneration (ballooning, Mallory hyaline) and mixed inflammatory cell infiltration. While much is understood about the relationship of steatosis to metabolic factors (over-nutrition, insulin resistance, hyperglycemia, metabolic syndrome, hypoadiponectinemia), less is known about inflammatory recruitment, despite its importance for the perpetuation of liver injury and fibrogenesis. In this review, we present evidence that liver inflammation has prognostic significance in NAFLD. We then consider the origins and components of liver inflammation in NASH. Hepatocytes injured by toxic lipid molecules (lipotoxicity) play a central role in the recruitment of innate immunity involving Toll-like receptors (TLRs), Kupffer cells (KCs), lymphocytes and neutrophils and possibly inflammasome. The key pro-inflammatory signaling pathways in NASH are nuclear factor-kappa B (NF-κB) and c-Jun N-terminal kinase (JNK). The downstream effectors include adhesion molecules, chemokines, cytokines and the activation of cell death pathways leading to apoptosis. The upstream activators of NF-κB and JNK are more contentious and may depend on the experimental model used. TLRs are strong contenders. It remains possible that inflammation in NASH originates outside the liver and in the gut microbiota that prime KC/TLR responses, inflamed adipose tissue and circulating inflammatory cells. We briefly review these mechanistic considerations and project their implications for the effective treatment of NASH. (Gut Liver 2012;6:149-171)

Key Words: Non-alcoholic fatty liver disease; Hepatic fibrosis; Non-alcoholic steatohepatitis

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the commonest form of liver disease in all regions of the world with modern industrialised economies, including Korea and many other Asian countries. Patients usually present without symptoms or clinical features are non-specific. Instead, liver abnormalities are found incidentally by hepatic imaging, particularly ultrasonography, and/or there are raised liver enzymes (alanine aminotransferase [ALT] and gamma-glutamyltranspeptidase). The diagnosis of NAFLD requires exclusion of other disorders, particularly viral hepatitis, significant alcohol intake, and exposure to potentially hepatotoxic medications. By agreements such as the Asia-Pacific Guidelines on NAFLD, the term NAFLD is now retained for cases of fatty liver associated with metabolic complications of over-nutrition, usually with central obesity and overweight.

We and others have stressed that NAFLD is closely allied to pre-diabetes and metabolic syndrome. As recently reviewed, the evidence for this includes the strong risk factors for NAFLD posed by obesity, insulin resistance, glucose intolerance and one or more components of metabolic syndrome, and the corresponding strong risk for onset of type 2 diabetes and cardiovascular disease/events conferred by a fatty liver.

Community based studies from Korea, Japan and other areas in North Asia have been highly informative for understanding that NAFLD is not so much a “Western disease” as the inevitable result of changes in prosperity and lifestyle that have increased the prevalence of overweight/obesity, insulin resistance, type 2 diabetes and cardiovascular risk factors (clustered as metabolic syndrome). Thus the community prevalence of NAFLD in

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this region increased from less than 10% in the 1980s, through 10% to 20% in the 1990s, to current rates of 15% to 30% or higher.3,17

The known ethnic differences in metabolic complications of over-nutrition, such as insulin resistance, diabetes, metabolic syndrome and hyperadipocytopenia, are also consistent with the proposition that, like them, NAFLD is a genetic disorder.18,19

Thus, an encompassing concept for NAFLD pathogenesis is that it represents the outcome of genetically determined interactions between a changing environment and a susceptible host. In this case, the environmental factors include too much energy intake, particularly in the form of cheap, highly processed simple carbohydrates and saturated fats, and reduced levels of physical fitness resulting from sedentary lifestyles.20,21 Of particular interest to the present review, one prevalent genetic polymorphism predisposing to steatosis in overweight persons of European or Hispanic ancestry, PNPLA3, does not operate by increasing the risks of diabetes or metabolic syndrome.18,22-25 Instead, it correlates with serum ALT levels,26 reflecting liver injury or inflammation, and with more severely fibrotic liver disease in both NAFLD/non-alcoholic steatohepatitis (NASH) and alcoholic cirrhosis.27-28 This point emphasises that not all cases of NAFLD have the same implications for liver disease.

NAFLD embraces a pathological spectrum of liver disease, from cases of steatosis with virtually no evidence of hepatocellular injury or liver inflammation, often referred to as simple steatosis or "not NASH," through steatohepatitis (NASH), to cellular injury or liver inflammation, often referred to as simple metabolic disease.29-31 The latter are often complicated by portal hypertension and hepatic decompensation, and occasionally present with hepatocellular carcinoma (HCC).32 At this late stage, steatosis and liver inflammation may both have resolved; they are cases of "cryptogenic cirrhosis." As discussed next, natural history and clinical outcome studies based on community and liver clinic cohorts indicate a nearly 2-fold increase in standardized mortality rates among persons with NAFLD.33,34 Further, while cardiovascular disease and common cancers remain the two most common causes of death, liver-related mortality ranks the third most common, as compared to 13th in the general community.35 A key question emerges: what aspects of liver pathology, and what disease mechanisms, account for progression of NAFLD to cirrhosis and its fatal complications?

WHICH ASPECTS OF NAFLD PATHOLOGY HAVE PROGNOSTIC AND MANAGEMENT IMPLICATIONS

1. Fibrotic severity

The observation that histologic characteristics are useful in predicting the outcome of patients with NAFLD is best exemplified for patients at either end of the pathological spectrum. At one end, individuals with only hepatic steatosis (simple steatosis) infrequently show signs of any histologic progression, and are not at significant long-term risk of liver-related death.12,13,14,36 By contrast, those with advanced hepatic fibrosis (bridging fibrosis [F3] and/or cirrhosis [F4]) are likely, in time, to experience liver-related complications (ascites, variceal bleeding, and/or HCC).35-37 While cardiovascular disease and cancer head the list of causes of death, 7- to 10-year liver-related mortality (12% to 25%) ranks third overall.35-37 In fact, the outcome of patients with advanced NAFLD (Child-Pugh B and C) is similar to that of individuals with hepatitis C virus-related cirrhosis.9,17

In reaching these general conclusions, certain assumptions are implied. First, the necessity for histologic appraisal is problematic because liver biopsies are performed less often outside research studies and clinical trials due to patient and clinician perceptions that the result will not influence management, and the concerns about biopsy-related complications. While non-invasive assessment of hepatic necroinflammatory activity and hepatic fibrosis (serum biomarkers, transient elastography) is increasingly advocated,29-41 it is most reliable at either end of the clinical spectrum of severity (mild, severe), when histology is most predictable. It remains suboptimal in the substantial number of patients in patients with mild-moderate hepatic fibrosis (F1, F2), among whom liver disease may progress.38

Second, in patients with only hepatic steatosis there can be changes in host characteristics over time, such as increasing body weight or worsening insulin resistance and/or development of diabetes, and baseline steatosis and necroinflammatory severity have not been correlated with such progression of metabolic disease.12,13 These considerations notwithstanding, most gastroenterologists and hepatologist would generally reassure patients with isolated hepatic steatosis about their liver prognosis, but recommend primary care follow-up of cardiovascular risk factors and lifestyle interventions to address these. Conversely patients with advanced hepatic fibrosis should enter a more rigorous liver follow-up protocol.

2. Presence of NASH (versus “not NASH”)

Current uncertainty about how “progressive” this condition really is at least partly stems from the use of differing operational definitions for NASH.45,46 Thus, NASH has been variously defined to include cases with hepatic steatosis and lobular inflammation (regardless of hepatic fibrosis),29 hepatic steatosis with lobular inflammation and ballooning of hepatocytes with or without fibrosis,24,47-48 or as separate scoring systems for “activity” (the NAFLD activity score, which assigns numerical scores to steatosis, lobular inflammation and ballooning and fibrosis [the latter usually F0-F4]).29 The Brunt system29 was developed by correlating histologic changes with serum aminotransferases (A1) as a measure of hepatic necroinflammatory activity, and not with clinical outcome, whereas the scoring system proposal by Kleiner et al.29 was never intended for diagnosis but was to be used as a tool for assessing serial liver biopsies in clinical trials. The premise has been that small changes could be identified more clearly and reliably by assigning numerical values than by