1 Non-alcoholic fatty liver disease: Hype or harm?

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LEARNING POINTS

- Non-alcoholic fatty liver (NAFL) often presents the clinician with a conundrum in deciding the significance of the problem.
- It is now widely recognized that non-alcoholic steatohepatitis (NASH) can progress to advanced liver disease evident as cirrhosis with all of its attendant complications including portal hypertension and hepatocellular cancer, and sometimes this progression is associated with the perplexing loss of histological hallmarks of the antecedent process of steatohepatitis.
- The challenge to clinicians is to discern NASH from the relatively more stable forms of fatty liver, which we prefer to call non-NASH fatty liver (NNFL).
- Therapy of NASH is evolving and aside from common conservative measures like exercise and diet treatment is likely to involve drug therapy with potential side effects. Thus refining the prognosis and discerning harm from hype will be increasingly important.
- Additional areas of special need for further study include what is sometimes referred to as "BASH," which indicates the presence of metabolic risks such as obesity and insulin resistance and the use of ethanol above safe levels but below levels at which the risk of alcoholic steatohepatitis (ASH) rises steeply.

Few potentially fatal diseases have ever been referred to as "trash" in a serious and critical treatise on the topic [1] or have been specifically the subject of an unsuccessful legal action aimed at shutting down a particular form of animal-derived food production (Caldwell S, personal experience) or have at one time been, rather accurately, referred to as "big" and "little" varieties to indicate early recognized variability in severity from mild and essentially inconsequential to potentially fatal (McCullough AJ, personal communication). However, all of these attributes are true of non-alcoholic fatty liver disease (NAFLD) and its potentially more severe subset non-alcoholic steatohepatitis (NASH).

In many ways, NASH remains a very challenging disorder over 30 years after pathologist Jurgen Ludwig first coined the term "NASH" for a "hitherto unnamed" form of steatohepatitis [2], and in doing so, he and his colleagues ushered in the modern era of clinical and basic research into the various forms of nonalcohol-related fatty liver—a field that has grown from a few published papers per year to many publications per week or month. On a practical level, much of the persistent challenge hinges on questions about the natural history and prognosis of fatty liver when it is encountered in a given individual—currently an almost daily occurrence in many clinics whether on its own or in combination with other liver disorders. The patient usually presents with asymptomatic, mild to moderate range of abnormal liver enzymes, negative additional diagnostic testing, and fatty changes noted on diagnostic ultrasound. This raises a frequent clinical question: is fatty liver a benign physiological finding (possibly an ancient adaptation to feast or famine, where nowadays feast exceeds famine), is it a disease warranting liver biopsy (with inherent risk) and directed intervention, or is it an epiphenomenon of a metabolic disorder encompassing diabetes mellitus, vascular disease, and cancer risks with clinical consequences that supersede the significance of the fatty liver [3]? All of these posits have some truth in NAFLD/NASH

Clinical Dilemmas in Non-Alcoholic Fatty Liver Disease, First Edition. Edited by Roger Williams and Simon D. Taylor-Robinson.

and constitute the pressing clinical challenge to discern hype and harm.

"Big" NASH and "little" NASH are now somewhat forgotten terms used casually in the discussion of early natural history studies, which indicated a dichotomy in the clinical course: long-term stability of the liver in many patients and progression to cirrhosis and liver-related mortality in a smaller but substantial fraction [4]. Since those early days, the nomenclature has obviously evolved with recognition of potentially progressive "big" NASH, characterized by cellular injury and fibrosis, as a subset of the more global term, NAFLD, which indicates liver fat exceeding 5–10% triglyceride by weight. Subsequently, long-term natural history studies of NAFLD have consistently demonstrated this dichotomous natural history: non-NASH fatty liver tends to be stable over years with low liver-related mortality, while NASH carries a significant, tangible risk of progression to cirrhosis and associated liver-related mortality [5–8]. Most of these studies have focused on mortality rather than morbidity, and overall mortality is clearly dominated by cardiovascular disease and nonliver malignancy. These findings suggest that the emphasis on the liver disease itself may be somewhat misplaced. However, this overlooks the fact that a substantial number of patients, especially those with histological NASH will progress to cirrhosis and suffer many of the typical cirrhosis-related complications. Moreover, the development of cirrhosis and coexisting vascular disease or neoplasm significantly complicates the management of either condition. Thus, directing specific therapy at the liver is appropriate in some patients, but careful patient selection is essential, and unless a therapy is very safe and inexpensive (such as diet and exercise), many NAFLD patients warrant only conservative management. Riskier interventions should be directed at those with histological NASH especially with more advanced fibrosis stages.

Is steatosis ever physiologically adaptive? To some extent it can be viewed as such under certain circumstances [9]. This is most evident in certain species of migratory *Palmipedes* spp. (geese and ducks) where the development of steatosis is a normal premigratory process and presumably provides a source of energy during the long flight with little calorie intake. This process was recognized long ago, and for thousands of years, "foie gras" production has hinged on it. However, our own work in cooperation with several individuals in France demonstrated that the *Palmipedes* develop only non-NASH fatty liver. Hence, the effort by People for the Ethical Treatment of Animals (PETA) to block foie gras production in the United States—on the grounds that the meat represented a disease state—failed due to the absence of NASH. No doubt, the grounds for the attempted legal action were the result of some of the media publicity that has surrounded NAFLD.

On the other hand, humans with histological NASH are at risk for progression of fibrosis through stages to cirrhosis. Serial biopsy studies suggest that this is a slow, steady march when it occurs [10]. However, it remains unclear whether or not the progression is uniform over time, and it is conceivable that NASH progression may occur in subclinical "fits and starts" with peaks and troughs of disease activity rather than by a slow, steady process. It has also been shown that some patients with non-NASH fatty liver may transition to histological NASH [11]. Presumably, changes in activity, diet, or weight with resultant worsening insulin resistance may trigger such a transition. Once cirrhosis develops in patients with NASH, complications of portal hypertension develop at a steady rate but somewhat slower than that seen with cirrhosis due to hepatitis C [12]. Patients are also at significantly increased risk of hepatocellular cancer usually, but perhaps not always, in the setting of coexisting cirrhosis [13].

Adding to the clinical diagnostic challenge, when cirrhosis develops in NASH, steatosis, a hallmark of NASH, tends to diminish significantly, sometimes leaving a picture of "cryptogenic cirrhosis," especially in patients without a confirmed antecedent diagnosis of NASH [14–16]. Such patients often present with minor findings, such as asymptomatic and previously unexplained thrombocytopenia, often labeled in prior encounters as idiopathic thrombocytopenia purpura ("ITP") or with cirrhosis, incidentally discovered at the time of elective surgery, especially for suspected or confirmed gallbladder disease. The mechanisms underlying diminished liver fat remain uncertain but may involve altered insulin exposure through changes in blood flow or repopulation of the liver from stem cells with altered physiology and fat metabolic capacity. Clearly, there are also other causes of cryptogenic cirrhosis, including silent autoimmune hepatitis, occult ethanol abuse, or as yet unrecognized viral infection, but NASH appears to be the leading etiology in many areas of the world [17].

Although it is well established that NAFLD has a largely dichotomous natural history, based on initial histology (NASH vs. non-NASH fatty liver), it is perplexing that certain aspects of NASH histology remain challenging.

While there are a number of characteristic histological findings, the key features that usually are used to define NASH are steatosis, inflammation, cellular ballooning, and fibrosis; the first three of these parameters define the commonly utilized NAFLD activity score (NAS) [18, 19]. Perhaps not surprisingly, histological fibrosis appears to be a reliable finding with low interobserver variation rates and a reliable indicator of prognosis. However, agreement between scoring systems and individual parameters remains a potentially significant problem that can muddy clinical trials and natural history studies [20–22]. Defining criteria for cellular ballooning has been especially problematic although emergence of keratin staining as a means of characterizing pathological processes within these cells may lead to beneficial refinements of histological criteria [23–26].

ASH, NASH, BASH (indicating both alcohol exposure and risks for metabolic fatty liver), chemical-associated steatohepatitis (CASH), and drug-associated steatohepatitis (DASH): the nomenclature for the recognized varieties of steatohepatitis has continued to evolve over the years [27]. While by no means uniformly accepted, the term "BASH" ("B" for both alcohol and metabolic fatty liver) denotes possibly the most significant of these, as it indicates the presence of metabolic risks for NASH such as obesity, diabetes, and inactivity together with ethanol use above safe levels but below levels at which the risk of ASH rises steeply [28]. This represents a potentially important gray area, and it highlights the fact that the diagnosis of "NASH" is truly both a clinical- and pathology-based exercises that is not always clear cut [29, 30].

What about the individual patient who is seen in the clinic and presents with the "chief complaint" of abnormal liver enzymes, negative additional testing, and fatty changes on diagnostic ultrasound? Is it a benign finding, a marker for comorbid vascular disease and cancer risk, or a disease warranting liver biopsy and more aggressive therapeutic management recommendations than diet and exercise? Recent advances in genetic risks promise to further help sort hype from harm in NAFLD. PNPLA3 and TM6SF2 polymorphisms code for gene products that appear to be intimately involved with small fat droplet and lipoprotein metabolism and impart significant risk for steatosis and related organ injury [31–34]. Although far from being available as clinical tools, this work points out the continued clinical importance of the family history in NASH/NAFLD [35]. Indeed, we recommend earlier consideration of biopsy when, as often is the case, a family member is significantly affected even if the relative was reported to have had alcohol-related liver disease. Moreover, preliminary work from our group suggests that PNPLA3 polymorphism may predict response to such mild agents as omega-3 fatty acid supplements.

Clearly, NASH progresses to advanced stages of fibrosis, cirrhosis, and hepatocellular cancer reasonably often, and it may shed some its histological hallmarks in the process, which can complicate the diagnosis. Recognition of this phenomenon has allowed clinicians to avoid Dr. Ludwig's "embarrassment" in diligently attempting to ferret out the occult alcoholic when actually confronted with frank NASH. Without doubt, the emergence of this field coexists with a degree of hype, which has likely been magnified due to the parallel obesity epidemic. It is all the more important to sort out, within the limitations of existing literature, the hype from the harm in order to best tailor emerging pharmacological treatment strategies and match risks and benefits.

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