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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Alcoholic, Nonalcoholic, and Toxicant-Associated Steatohepatitis: Mechanistic Similarities and Differences

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SUMMARY

This article reviews selected important mechanistic similarities and differences in alcoholic steatohepatitis, nonalcoholic steatohepatitis, and toxicant-associated steatohepatitis.

Hepatic steatosis and steatohepatitis are common histologic findings that can be caused by multiple etiologies. The three most frequent causes for steatosis/steatohepatitis are alcohol (alcoholic steatohepatitis, ASH), obesity/metabolic syndrome (nonalcoholic steatohepatitis, NASH), and environmental toxicants (toxicant-associated steatohepatitis, TASH). Hepatic steatosis is an early occurrence in all three forms of liver disease, and they often share common pathways to disease progression/severity. Disease progression is a result of both direct effects on the liver as well as indirect alterations in other organs/tissues such as intestine, adipose tissue, and the immune system. Although the three liver diseases (ASH, NASH, and TASH) share many common pathogenic mechanisms, they also exhibit distinct differences. Both shared and divergent mechanisms can be potential therapeutic targets. This review provides an overview of selected important mechanistic similarities and differences in ASH, NASH, and TASH. ***(Cell Mol Gastroenterol Hepatol 2015;1:356–367; http://dx.doi.org/10.1016/j.jcmgh.2015.05.006)***

Keywords: Alcoholic Steatohepatitis; Mechanisms; Nonalcoholic Steatohepatitis; Toxicant-Associated Steatohepatitis.

Hepatic steatosis and steatohepatitis are common histologic findings that can be caused by multiple etiologies (Figure 1). The three most frequent causes for steatosis/steatohepatitis are alcohol, obesity/metabolic syndrome, and environmental toxicants, as reviewed herein.

Alcohol remains one of the most common causes of both acute and chronic liver disease in the United States.[1] In Western countries, up to 50% of cases of end-stage liver disease have alcohol as a major etiologic factor.[2] Excessive alcohol consumption is the third leading preventable cause of death in the United States. Alcohol-related deaths, excluding accidents/homicides, accounted for 22,073 deaths in the United States in 2006, with 13,000 of those specifically attributed to alcoholic liver disease (ALD).[3] Cirrhosis from any cause represents the 12th leading cause of death in the United States, and 45.9% of all cirrhosis deaths are attributed to alcohol.[4] As shown by early studies involving controlled drinking with subsequent liver biopsies in volunteers, almost everyone who drinks heavily for 12 weeks will develop fatty liver.[5,6] This usually resolves with abstinence, but a subset of people who continue to drink heavily will develop alcoholic hepatitis, which may progress to cirrhosis or even hepatocellular carcinoma (HCC).

The progression of ALD is somewhat similar to nonalcoholic fatty liver disease (NAFLD) and toxicant-associated fatty liver disease (TAFLD) in that it generally occurs over several years. Importantly, studies from the Veterans Administration (VA) have shown that patients with cirrhosis and superimposed alcoholic hepatitis had >60% mortality over a 4-year period, with most of those deaths occurring in the first few months.[7] Thus, the prognosis for this aggressive stage of ALD is worse than for many common types of cancer, such as breast, prostate, and colon.

We have known that hepatic steatosis is associated with obesity since at least the 1950s. However, it was not until 1980, when Ludwig et al[8] coined the term "nonalcoholic steatohepatitis—NASH" to describe this previously unnamed condition that often occurred in cirrhotic patients, that its clinical importance became recognized. NAFLD encompasses a pathologic spectrum of liver disease that ranges from steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma. NAFLD is by far the most common

Abbreviations used in this paper: **ALD, alcoholic liver disease; ALT, alanine aminotransferase; ASH, alcoholic steatohepatitis; AST, aspartate transaminase; BMI, body mass index; CYP2E1, cytochrome P450 isoform 2E1; ECM, extracellular matrix; ER, endoplasmic reticulum; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; HSC, hepatic stellate cell; IL, interleukin; LA, linoleic acid; LPS, lipopolysaccharide; miR, microRNA; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NK, natural killer; NKT, natural killer T; OXLAM, oxidized linoleic acid metabolite; PAI-1, plasminogen activator inhibitor-1; PCB153, 2,2′,4,4′,5,5′-hexachlorobiphenyl; PPAR, peroxisome proliferator-activated receptor; RNS, reactive nitrogen species; SNP, single-nucleotide polymorphism; TASH, toxicant-associated steatohepatitis; TAFLD, toxicant-associated fatty liver disease; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; T_H, helper T cell; TLR, Toll-like receptor; TNF, tumor necrosis factor; VA, U.S. Department of Veterans Affairs/Veterans Administration.**

2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2015.05.006

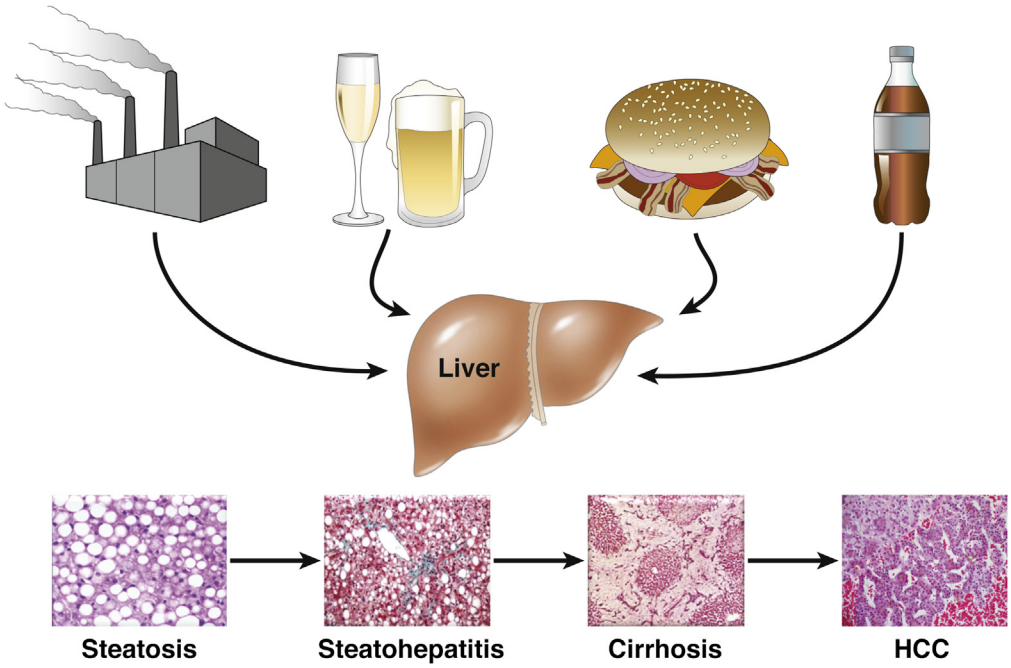

Figure 1. Multiple etiologic factors and metabolic pathways lead to the same histologic liver abnormalities.

cause of liver disease and abnormal enzymes in children and adults in the United States, with about one-third of adults thought to have NAFLD. The U.S. unselected prevalence of NASH is estimated to be 2% to 5%. Dietary factors, including high-fat and high-fructose diets, have been associated with the development of NASH.

Over 60 million unique chemicals were registered with the Chemical Abstracts Service Registry as of May 2011. With the rapid pace of new chemical discovery and commercialization, it is impossible to fully define the potential impact of these substances on the liver. However, the problem appears significant: 33% of the 677 most common workplace chemicals reported in the National Institute of Occupational Safety and Health Pocket Guide are associated with hepatotoxicity.[9] We first coined the term toxicant-associated steatohepatitis (TASH) in 2010, related to a cohort of patients with high vinyl chloride exposure who had classic steatohepatitis on liver biopsy but were not obese and did not drink alcohol.[10] Many classes of industrial chemicals have been associated with steatosis or steatohepatitis. These include (but are not limited to): solvents and other halogenated hydrocarbons, volatile organic mixtures, persistent organic pollutants, pesticides, and some nitro-organic compounds.[11] Recently enacted federal legislation (the Janey Ensminger Act of 2012) mandates medical coverage through the Department of Veteran's Affairs for hepatic steatosis in military personnel who were exposed to solvents in the drinking water at Marine Corps Base Camp Lejeune.[12] In addition to exposure level, an individual's susceptibility to chemical-induced liver disease is determined by polymorphisms in the genes of xenobiotic metabolism, concomitant use of alcohol or prescription medications, nutritional factors, and obesity—as many organic chemicals are lipid soluble.

This article reviews the mechanisms for the development of steatohepatitis, highlighting mechanistic differences as well as many common pathways between the three major etiologies (Table 1). For example, alcohol and the environmental toxicant vinyl chloride are both metabolized through cytochrome P450 2E1 (CYP2E1) to form toxic aldehyde intermediates. Moreover, fructose is also metabolized to an aldehyde. Thus, three divergent forms of steatohepatitis can have an aldehyde as an intermediate. On the other hand, dietary unsaturated fat may play a protective role in NASH, but n-6 unsaturated fat appears to augment ALD. There can also be major interactions between types of steatohepatitis. For example, high-fat feeding and subsequent NASH markedly reduces glutathione *S*-transferases, which play a protective role against a variety of environmental toxicants and alcohol. This review evaluates selected mechanistic similarities and differences in alcoholic steatohepatitis (ASH), NASH, and TASH.

Mechanisms of Liver Disease

Nutritional Abnormalities

Moderate/severe alcoholic hepatitis is usually associated with malnutrition. In large VA cooperative studies, virtually every patient with alcoholic hepatitis had some degree of malnutrition.[13] Almost 50% of patients' energy intake came from alcohol. Although their calorie intake was frequently adequate, their intake of protein and critical micronutrients was often deficient. A classic example of micronutrient deficiency is zinc deficiency.[14,15] Alcoholics regularly have decreased dietary intake of zinc as well as poor absorption and increased excretion. Moreover, oxidative stress causes zinc to be released from critical zinc-finger proteins. The cumulative negative