Metabolic Manifestations of Hepatitis C Virus

Diabetes Mellitus, Dyslipidemia

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KEYWORDS

• Hepatitis C • Steatosis • Hypobetalipoproteinemia
• Microsomal triglyceride transfer protein • Insulin resistance • Tumor necrosis factor

KEY POINTS

- Out of excessive alcohol consumption, steatosis should be classified into 2 types according to hepatitis C virus (HCV) genotypes: metabolic steatosis, which is associated with features of metabolic syndrome and insulin resistance in patients infected with nongenotype 3, and viral steatosis, which is correlated with viral load and hyperlipemia in patients infected with genotype 3.
- HCV interacts with host lipid metabolism by several mechanisms, such as promotion of lipogenesis, reduction of fatty acid oxidation, and decreases of lipids export, leading to hepatic steatosis and hypolipidemia.
- A strong link between HCV infection and diabetes mellitus has been found in subject-based studies and, to a lesser degree, in population-based studies.
- HCV-mediated insulin resistance may be promoted through multiple pathogenic mechanisms, such as direct inhibition of insulin signaling pathway by HCV core protein in the liver, overproduction of tumor necrosis factor-alpha, oxidative stress, modulation of incretins, or pancreatic ß-cells dysfunction.

Metabolic disorders are common in patients with chronic hepatitis C (CHC) virus (HCV) infection. In a nationwide population-based register study conducted in Sweden, type 2 diabetes was the second cause of extrahepatic disease among patients with CHC and its prevalence was twice higher than that reported in the general population (10.6 vs 5.5%, $P<.05$).[1] According to a meta-analysis on extrahepatic manifestations of hepatitis C, conservative estimates suggest that as many 402,000 patients in the

Disclosure: Dr L. Serfaty serves on consulting committees, advisory committees, or review panels for AbbVie, Janssen, Merck Sharp & Dohme (MSD), Roche, Bristol-Meyers Squibb (BMS), Gilead, and performs speaking and teaching for Roche, AbbVie, MSD, Gilead, BMS, and Janssen.

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Clin Liver Dis ■ (2017) ■–■
http://dx.doi.org/10.1016/j.cld.2017.03.004 **liver.theclinics.com**

United States have HCV-associated diabetes mellitus.[2] Several experimental and clinical studies have provided evidence that HCV itself is able to promote insulin resistance (IR) through multiple pathogenic mechanisms, including impairment of the insulin signaling pathway.[3] There is also considerable evidence for an overprevalence of lipid disorders and steatosis in patients with CHC, suggesting close relationship with HCV infection.[3] In this setting, chronic HCV infection can be considered a metabolic disease in view of its interaction with lipid metabolism leading to steatosis, as well as its impairment of glucose metabolism leading to IR and diabetes. This article examines the relationship between HCV, lipid abnormalities, steatosis, IR, and diabetes, as well as the pathogenic mechanisms accounting for these events in persons infected with HCV. The impact of these metabolic disorders on the natural course of CHC will not be discussed.

HEPATITIS C VIRUS, LIPID METABOLISM, AND HEPATIC STEATOSIS

Hepatitis C Virus–Related Steatosis: Prevalence and Risk Factors

In CHC patients, the prevalence of steatosis ranges from 40% to 86% (mean 55%), which is higher than in the general population (20%–30%) or in patients with other chronic liver disease (19%–50%), including chronic hepatitis B.[4,5] Most patients have mild steatosis affecting less than 30% of hepatocytes with a pattern of distribution in the periportal region of the liver, whereas the centrilobular region is mainly affected in nonalcoholic steatohepatitis patients.[6] Out of excessive alcohol consumption, steatosis should be classified into 2 types according to HCV genotypes: metabolic steatosis, which is associated with features of metabolic syndrome and IR in patients infected with nongenotype 3, and viral steatosis, which is correlated with viral load and hypolipidemia in patients infected with genotype 3.[7] Compared with other genotypes, infection with genotype 3 is associated with higher prevalence and more severe steatosis in 73% versus 50%, and moderate to severe steatosis in 40% versus 10% to 15%, respectively.[4] Furthermore, the severity of steatosis in patients infected with genotype 3 is inversely related with cholesterol and apolipoprotein B lipoprotein serum levels, defining in some cases hypobetalipoproteinemia.[5] Antiviral treatment is able to reverse this hypobetalipoproteinemia concomitantly with significant reduction of steatosis.[4,5,8] In patients infected with nongenotype 3, genetic background, such as interleukin and patatin-like phospholipase-3 (PNPLA3) polymorphisms, is associated with HCV-related steatosis.[9,10] In the era of new direct antiviral agents (DAAs) regimen, the role of viral-related steatosis has been suggested for the lower efficacy of antiviral treatment in patients infected with genotype 3.[11] In this setting, intrahepatic fat sequestration by the replicating virus may reduce access to DAAs and reduce their efficacy. Specific studies are needed to evaluate the impact of HCV-related steatosis on the efficacy of DAAs.

Pathogenic Mechanisms of Hepatitis C Virus–Related Steatosis

The HCV life cycle is closely associated with lipid droplets and lipoprotein metabolism in hepatocytes.[12,13] HCV interacts with host lipid metabolism by several mechanisms, such as promotion of lipogenesis, reduction of fatty acid oxidation, and decreases of lipids export, leading to hepatic steatosis and hypolipidemia. In transgenic mouse model, it has been shown that HCV core protein that promotes steatosis is able to inhibit both the microsomal triglyceride transfer protein (MTTP) activity and very low density lipoprotein secretion,[14] to impair the expression of peroxisome proliferator-activated receptor $(PPAR)_{\gamma}$,[15] and to induce hepatic gene expression and transcriptional activity of sterol response element binding protein (SREBP)-1.[16] Elevated