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Metabolic Aspects of Hepatitis C Virus

Metabolic Aspects of HCV

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Abstract

Many metabolic factors are associated with chronic HCV (CHC) infection and can influence the course of the illness and impact the progression of liver and non-liver-related diseases through complex interactions. Several of these factors impact the course of CHC and result in the conceptual translation of CHC from a localized to systemic disease. Besides the traditional liver manifestations associated with CHC infection, such as cirrhosis and hepatocellular carcinoma, various extrahepatic disorders are associated with Hepatitis C virus (HCV) infection, including atherosclerosis, glucose and lipid metabolic disturbances, alterations in the iron metabolic pathways, and lymphoproliferative diseases.

The coexistence of metabolic disorders and CHC is known to influence the chronicity and virulence of HCV and accelerates the progression to liver fibrosis and hepatocellular carcinoma (HCC). Insulin resistance is one of the key factors that have a tremendous metabolic impact on CHC. Therefore, there is a great need to properly evaluate patients with CHC infection and correct the modifiable metabolic risk factors. Furthermore, patients with HCV who achieved a sustained virological response (SVR) showed an overall improvement in glucose metabolism, but the exact evidence still requires further studies with long-term follow-up. This review delineates the most recent evidence on the main metabolic factors associated with CHC and the possible influence of chronic HCV infection on metabolic features.

Key Words: Hepatitis C Virus; Metabolic factors; Steatosis; Insulin resistance

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Core Tip:

HCV infection has several metabolic aspects that are largely well understood; as such, HCV is nowadays considered a systemic disease rather than a local disease with
different metabolic consequences. Moreover, these metabolic factors may affect the natural history of chronic liver disease and of diseases not related to the liver, which constitute a significant burden on the overall health of the human body, with an increased economic burden to patients, healthcare systems, and society if not adequately addressed and appropriately managed. More studies are needed to evaluate metabolic aspects associated with HCV infection and delineate their effects and the long-term outcome of antiviral therapies.

INTRODUCTION

Hepatitis C virus (HCV) infection is considered one of the most notable causes of chronic liver disease worldwide.¹ Not only does HCV infection confer the risk of developing chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC), it also has many extrahepatic manifestations, such as disorders of glucose and lipid metabolism, polyarthritis resembling rheumatoid arthritis, vascular atheromatous disease, mixed cryoglobulinemia, lymphoproliferative diseases, renal disorders, insulin resistance (IR), type 2 diabetes (T2DM), sicca syndrome, and autoimmune disorders.²⁴ There are several studies on the effect of metabolic factors on the natural history of patients with chronic hepatitis C.⁵ The deleterious effects of metabolic complications resulting from HCV infection are mainly related to glucose and lipid metabolism impairments.⁶

Given that it is a systemic disease, chronic HCV infection could influence the metabolic homeostasis of the host through several complex interactions, even in light of pre-existent metabolic status and genetic background.⁵ Several factors can accelerate the disease course from chronic HCV infection to cirrhosis and may impact the likelihood of achieving a sustained virological response (SVR) after receiving antiviral therapy. Among the reported factors are metabolic factors that may change the course of illness in chronic hepatitis C (CHC) patients and impact the results of antiviral treatment,⁷ despite the apparent improvement in HCV management results after the introduction of direct-acting antivirals compared with the previous standard of care interferon-based therapy.⁸⁹ Interestingly, this is not a “one-way street,” as chronic HCV infection can
have metabolic effects due to its influence on glucose and lipid metabolism, which impacts the host's metabolic homeostasis and may result in its extrahepatic sequela.\textsuperscript{10} The extrahepatic burden of HCV infection exceeds its effect on the liver as it is a significant burden on the overall health of the human body, causing increased economic burden to patients and healthcare systems.\textsuperscript{11,12}

We have discussed the most recent evidence on the main metabolic factors related to CHC, along with the proposed pathophysiological machineries essential to the correlation between HCV infection and metabolic disorders and the possible influence of chronic HCV infection on metabolic features.

**INSULIN RESISTANCE**

IR is considered a keystone of metabolic syndrome (MS) with increasing incidence worldwide, representing a major cause of morbidity and mortality.\textsuperscript{13} As reported in the literature, HCV infection is associated with IR in up to 80\% of cases; consequently, the risk of developing T2DM is found to be twice as high as in subjects without HCV.\textsuperscript{14,15} There is a high chance of coexistence between MS and CHC owing to many related host factors, such as the presence of visceral obesity; moreover, HCV infection itself is reported to affect glucosidic homeostasis, leading to hepatic and extrahepatic IR.\textsuperscript{1}

Moreover, CHC is found to increase the risk of developing metabolic diseases with these complications.\textsuperscript{16} IR in patients with CHC significantly impacts the severity and progression of chronic liver disease via direct and indirect effects by inducing steatosis.\textsuperscript{17} Meanwhile, steatosis activates stellate cells via collagenous deposition and the generation of lipid peroxides\textsuperscript{18}, which, in turn, promotes fibrogenesis via the direct activation of hepatic stellate cells, tumor necrosis factor-\(\alpha\) and connective growth factor production, and ductular reactions induction.\textsuperscript{19} In this context, a high prevalence of cirrhosis and non-SVR was observed among patients with diabetes and CHC with an observed lower rate of SVR in patients with insulin resistance, not only in interferon-based treatment.\textsuperscript{7}
Moreover, there is a reported association between IR and the presence of esophageal varices in patients with HCV-related compensated cirrhosis. The potential of insulin to control dynamic components of portal hypertension, such as endothelial nitric oxide and endothelin production, might explain this. Not only are IR and DM are more prevalent in the course of HCV infection, but they also occur post-liver transplantation in patients with CHC infection. It's not surprising, then, that T2D is linked to a three-fold increased risk of HCC, with a higher risk seen in patients who have both HCV and T2D; this could be due to the possible molecular mechanisms and intermediaries involved in hepatic carcinogenesis, such as IR and hyperinsulinemia, oxidative stress, and reported cytokine imbalances between proinflammatory and anti-inflammatory cytokines. Several studies have reported the impact of IR and steatosis and both rapid (RVR) and sustained (SVR) in patients with CHC treated with antiviral therapy; the plausible explanations that IR and steatosis may affect the response to antiviral therapy and the reasons for the disparities in results might be due to pre-existing variances in metabolic dysfunctions and genetic diversities among the tested groups. Other studies reported the efficiency of proper glucose control in HCV infected patients that improve early after antiviral treatment, with benefits that are not restricted to the diabetic patient only furthermore, achievement of SVR by DAAs to eliminate HCV improves their glycemic control with a possible reduction on the faster progression of hepatic fibrosis.

Also, treatment of HCV with DAAs found to improve steatosis, hepatic inflammation, and the nutritional status in most of the studied patients. This explains how profound and widespread effects of the impairment of insulin pathways exerted by HCV infection and vice versa. Consequently, further evidence from long-term follow-up studies is still required to determine if successful eradication of HCV can help to ameliorate IR and improve glycemic control and clinical outcomes in patients with established DM.

STEATOSIS
In individuals with CHC, hepatic steatosis is a frequent histological finding, with a frequency of up to 80%, which is higher than that in noninfected individuals; thus, it is considered as a distinct entity in the setting of HCV viral infection with specific clinical and prognostic implications. Not only viral factors are responsible for steatosis in patients with CHC, but there are also different common risk factors for steatosis, such as obesity, T2D, alcohol, and dyslipidemia, which are common in the examined cohorts. Specific genotypes of HCV, especially the HCV genotype 3, are more correlated with hepatic steatosis; moreover, HCV has the ability to promote the intracytoplasmic deposition of fat in the liver by enhancing hepatic fatty acid production and decreasing lipid release and breakdown processes, both directly and indirectly. Interestingly, steatosis has also been related to HCV viral load and was found to decrease after SVR was achieved. Many studies reported that steatosis could be a predictor of liver fibrosis in patients with CHC; additionally, in untreated CHC patients, worsening of steatosis may be an independent factor related with the advancement of liver fibrosis. This could be explained by "viral" and "metabolic" steatosis, in which elevated insulin levels and inflammatory mediators on liver stellate cells promote the advancement of fibrosis and liver disease. Steatosis may improve and even vanish following effective antiviral treatment with interferon and ribavirin, according to some reports; however, evidence for a similar effect of direct-acting antivirals is currently limited.

In contrast, cross-sectional and longitudinal studies have shown that despite achieving SVR during CHC treatment, some patients have been found with clinically significant steatosis and fibrosis. In this clinical setting, many studies reported the association between steatosis in fatty liver and HCC development in patients with CHC.

**VISCERAL OBESITY**

In the context of steatosis and IR, visceral obesity has been associated with liver fat accumulation in healthy subjects and is also related to viral load. Several studies have discussed the association between HCV RNA status and obesity.
Plausible explanations include the feasibility of adipose tissue to promote fatty substrates and a proinflammatory status that accelerate HCV replication; moreover, the ability of HCV to interfere with adipocyte function through indirect methods, and increase the inflammatory status or via a direct mechanism that helps to increase the colonizing adipocytes and immune cells infiltrating adipose tissue. Further studies are needed to delineate the potential role of obesity in affecting SVR rates after treatment with antiviral agents.

**LIPID METABOLISM**

HCV infection is involved in disrupted lipoprotein homeostasis via impairment of the very low-density lipoprotein levels (VLDL)-releasing pathway, which is one of the main causes of hepatic fat deposition. Several studies have discussed the relationship between lipoproteins and HCV cell cycle and found that patients with CHC have lower serum low-density lipoprotein levels (LDL), which are inversely associated with the severity of liver fibrosis; however, this is still a controversial issue. As reported by Riccardo et al, the average LDL levels increased significantly after viral eradication, although there were no effects on triglycerides and HDL. However, it is still debatable whether infections with HCV are linked to an increased risk of cardiovascular events such as carotid atherosclerosis, myocardial infarction, and heart attacks. Notably, studies reported that patients with CHC had more atherosclerosis, as measured by carotid artery plaques and/or intima-media thickness (IMT), than healthy controls; likewise, the frequency of asymptomatic carotid atherosclerosis was higher in patients with CHC than in matched controls.

HCV infection could be an independent risk factor for increased carotid IMT and cerebrovascular deaths, as reported in many types of study; this may be explained by the proinflammatory mechanisms that underlie liver fibrogenesis and could be systemically activated, leading to the promotion of atherosclerosis. In contrast, several published studies have failed to show the association between atherosclerosis and HCV
infection, even with an increased prevalence of IR in patients with HCV infection. Therefore, further studies are needed to validate those data.

**THE ROLE OF VITAMIN D**

25-Hydroxyvitamin D (25[OH]D) deficiency has been discovered in patients with CHC, even in those with minimal liver damage; however, some studies reported no association between vitamin D status and fibrosisstage. The role of vitamin D status in treatment regimens for HCV infection is still not well understood, although it is interesting that vitamin D3 supplement augments the response to antiviral therapy in infections with HCV genotypes 1-4, as reported in some randomized clinical trials.

**IRON METABOLISM**

It is debatable whether iron promotes or suppresses HCV viral replication, but it is considered a central component for HCV virus replication and translation. In patients with CHC, elevated serum ferritin and the associated increased iron load in liver were more evident and were considered a significant predictor for hepatic fibrosis progression. Hepcidin is a peptide hormone with an essential role in regulating iron levels under homeostatic states. Accordingly, iron metabolism alterations in CHC are related to the decreased hepcidin concentrations, although the exact underlying mechanisms remain unclear. Still, there is an urgent need for a better understanding of how HCV impacts iron metabolism and if it could be implemented to control disease advancement.

**SKELETAL MUSCLE**

It is well known that sarcopenia, increased intramyocellular lipid accumulation, myosteatosis, and reduced muscle mass are all connected with CHC infection, especially in the advanced stages. A high incidence rate of sarcopenia was reported, up to 70%, in patients with cirrhosis. Because of anabolic resistance, current nutritional supplementation methods have not been successful in reversing sarcopenia.
association between CHC infection of the liver and muscle loss is well documented. High BMI, IR, diabetes, hepatic steatosis, increased inflammation, increased oxidative stress, lipotoxicity, and multiple factors involved in muscle depletion all are considered as independent risk factors that predispose patients with CHC to skeletal muscle disorders.

REPRODUCTIVE STATUS AND MENOPAUSE
Several studies performed on pregnant women with HCV infection reported reduced necro-inflammatory activity, and the rate of fibrosis advancement in CHC is nearly twice as fast in males compared to females. Another report stated that long-term hormonal replacement therapy could prevent accelerated liver fibrosis in menopausal women with CHC. Noteworthy improvement in sexual dysfunction was reported in males and females after HCV treatment with direct-acting antivirals.

CONCLUSION
The eradication of HCV remains an essential target for preventing the progression of liver disease and improving or preventing HCV-related metabolic extrahepatic manifestations that have an essential role in morbidity and mortality, affecting the patient’s health-related quality of life.
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<td>&quot;Metabolic Factors and Chronic Hepatitis C: A Complex Interplay&quot;, 'Hindawi Limited', 2013</td>
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<td>assets.cureus.com</td>
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<td>Alessandro Gualerzi, Mattia Bellan, Carlo Smirne, Margherita Tran Minh et al. &quot;Improvement of insulin sensitivity in diabetic and non diabetic patients with chronic hepatitis C treated with direct antiviral agents&quot;, PLOS ONE, 2018</td>
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<td>5</td>
<td>Matthew T. Kitson, Gregory J. Dore, Jacob George, Peter Button et al. &quot;Vitamin D status does not predict sustained virologic response or fibrosis stage in chronic hepatitis C genotype 1 infection&quot;, Journal of Hepatology, 2013</td>
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