

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- α , oxidative stress, modulation of incretins, or pancreatic β -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

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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),¹⁵ and to induce hepatic gene expression and transcriptional activity of sterol response element binding protein (SREBP)-1.¹⁶ Elevated

lipogenesis and reduced cholesterol synthesis have been confirmed in patients with CHC compared with healthy controls.¹⁷ In HCV-infected human hepatoma (Huh)-7.5 cells, mitochondrial lipid β -oxidation is significantly attenuated, which results in low lipid combustion.¹⁸ Lipids accumulation seems depend on HCV genotype, as demonstrated in experimental models. Triglycerides accumulation only occurs in genotypes 1 or 3 transfected cells,¹⁹ although it is the greatest with genotype 3 core protein in transgenic mouse.²⁰ SREBP-1-dependent fatty acid synthase promoter activity and PPAR γ impairment are also greater with HCV genotype 3.^{20,21} In subjects receiving antiviral therapy, it has been shown that genotype 3 but not genotype 2 selectively interferes with the late cholesterol synthesis pathway and this distal interference was resolved with systemic vascular resistance.²² Finally, MTP may play a central role in HCV-related steatosis, mainly through hyperinsulinemia in nongenotype 3 infected patients, and by direct virus-related effects in patients infected with genotype 3.²³

HEPATITIS C VIRUS, TYPE 2 DIABETES, AND INSULIN RESISTANCE

Prevalence and Risk Factors

IR has been clinically defined as a condition in which cells become resistant to the action of insulin, such that the typical response to a defined amount of insulin is markedly diminished. The net result is that higher levels of insulin are needed to evoke the same cellular response. In humans, IR is thus evaluated by the ability of insulin to control glycaemia. Methods used to estimate IR include (1) fasting insulin concentration; (2) quantitative insulin sensitivity check index, which is calculated as $1/(\log [\text{fasting insulin}]1\log [\text{fasting glucose}])$; and (3) the homoeostasis model assessment (HOMA)-IR, calculated as $\text{insulin (mU/m)} \times (\text{fasting glucose [mmol/L]}/22.5)$; a 12-hour overnight fast is essential for the assessment of IR.²⁴ HOMA-IR is easily calculated using fasting insulin and fasting glucose but is poorly related to IR data obtained by the gold standard euglycemic hyperinsulinemic clamp.²⁵ The presence of IR has been defined as a HOMA value of greater than 4.65 or a value of greater than 3.60 in persons with a body mass index (BMI) of 427.5 kg/m^2 .²⁶

The link between HCV infection and type 2 diabetes has been evaluated in several studies with conflicting results according to the study population; that is, subject-based versus population-based study. In subjects with chronic liver disease, the prevalence of diabetes ranges between 13.6% and 67.4% in case of HCV infection, which is higher than that reported for subjects with other chronic liver diseases, such as chronic hepatitis B, independent of the stage of liver fibrosis (**Table 1**).^{27–33} In 2 meta-analyses, a significant relationship between HCV and diabetes was reported when compared with hepatitis B virus (HBV)-infected controls, with an adjusted odds ratio (OR) of 1.8 (95% CI 1.2–2.4) and 1.9 (95% CI 1.4–2.6), respectively.^{34,35} Among 462 nondiabetic CHC subjects, IR assessed by HOMA-IR greater than 3 was present in 32.4%, which was greater when compared with patients with chronic HBV matched for age, sex, BMI, and fibrosis score (35 vs 5%, $P < .0001$).³⁶ Multivariate analysis revealed that infection with genotypes 1 and 4 was a significant factor associated with IR in nondiabetic chronic HCV subjects (OR 2.984, $P < .001$). Other significant factors included age greater than 40 years, the presence of metabolic syndrome, extensive fibrosis, and severe steatosis. Moreover, IR was associated with a high serum viral load and HOMA-IR correlated significantly with serum HCV RNA level and necroinflammation, in this subgroup of subjects. The genotype specific association with IR has been found in another study.³⁷ The dose-dependent relationship between HCV viral load and IR, independent of visceral fat in one study, has been

Table 1
Prevalence of type 2 diabetes in hepatitis C virus–positive versus hepatitis C virus–negative subjects

Author (Reference)	Study Population (N)	HCV+ (%)	HCV– (%)
Alison et al, ²⁸ 1994	Cirrhosis (100)	50	9
Grimbert et al, ²⁹ 1996	Chronic viral disease (304)	24	9
Mason et al, ²⁷ 1999	Viral hepatitis (1117)	21	12
Caronia et al, ³⁰ 1999	Virus-related cirrhosis (1232)	24	9
Arao et al, ³¹ 2003	Viral hepatitis (866)	21	12
	Cirrhosis	31	12
Imazeki et al, ³² 2008	Viral hepatitis (952)	13.6	6.3
	HCV-cleared	—	9
Rouabhia et al, ³³ 2010	Viral hepatitis (416)	39.1	5
	Cirrhosis	67.4	20
Metha et al, ⁵² 2000	General population (9841) (Prevalence of HCV+: 2.1%) (Prevalence of diabetes: 8.4%)	NA Age >40 y: adjusted OR 3.77	NA
Montenegro et al, ⁵³ 2013	General population (2472) (Prevalence of HCV+: 26.2%)	10.1	7.5
Stepanova et al, ⁵⁴ 2012	General population (39,506) 1988–94 (15,866, HCV+ 1.95%) 1999–2004 (13,970, HCV+ 1.97%) 2005–2008 (9670, HCV+ 1.68%)	7.7 7.9 10.1	5.5 7.9 9.1
Younossi et al, ⁵⁵ 2013	General population (19,741) (Prevalence of rHCV+: 0.88%)	12.66	7.36
Ruhl et al, ⁵⁶ 2014	General population (15,128) (Prevalence of HCV+: 1.7%)	10.5	10.2
Schnier et al, ⁵⁷ 2016	General population (HCV+: 21,929) (Matched HCV–: 65,074)	2.9	2.9

confirmed in 2 additional studies.^{38,39} Conversely, the prevalence of HCV infection in diabetic subjects is higher than in the general population, ranging from 5% to 12% (Table 2).^{27,40–42} This statistical relationship could be the result of nosocomial risk in diabetic subjects. However, long-term follow-up population-based studies assessing the incidence of diabetes in large cohorts of subjects have shown the risk of developing diabetes was significantly higher in HCV subjects with risk factors such as age or obesity.^{43,44} In a longitudinal study of liver transplant recipients who were followed for 1 year, HCV-positive subjects were 4 times more likely to become diabetic after transplant than were HCV-negative subjects. In addition, HCV RNA levels correlated with a more rapid development of IR.⁴⁵ Steatosis, which is highly prevalent in CHC, may be another explanation for the link between HCV and IR. The absence of IR in subjects with viral steatosis indirectly suggests that steatosis is the consequence rather than the cause of IR in chronic HCV.^{6,7} Moderate iron overload is frequent in chronic HCV but there is no association between intrahepatic iron concentration and HOMA index.⁷ Association of IR with oxidative stress has been found in 1 study.⁴⁶ The association of IL-28 B polymorphism with IR has been suggested in HCV patients but with conflicting results.^{47,48} Finally, the improvement of IR in patients with HCV clearance following antiviral therapy suggests that HCV infection itself may promote IR.^{49,50} In this setting, a long-term follow-up study in nondiabetic HCV subjects receiving antiviral therapy has shown that SVR was associated with lower incidence of type 2 diabetes onset compared with non-SVR.⁵¹

However, despite the evidence in subject-based studies that HCV may promote IR and diabetes, the link between HCV and diabetes was not fully confirmed in population-based studies, mainly cross-sectional. The prevalence of type 2 diabetes in HCV-positive persons ranges between 2.9% and 12.6%, which was globally similar to that reported for HCV-negative persons and far lower than that reported for HCV subjects with chronic liver disease (see Table 1).^{52–57} In a study using National Health and Nutrition Examination Survey (NHANES) data, the relationship between HCV infection and diabetes was found significant among persons greater than 40 years of age.⁵² In another study using NHANES cycles, no association was found in NHANES 1999 to 2004 (OR 0.9, 95% CI 0.6–1.6) or NHANES 2005 to 2008 (OR 1.3, 95% CI 0.7–2.3), despite increased prevalence of diabetes in the later cycle.⁵⁴ In a second study using NHANES 1999 to 2010, the risk of having diabetes was twice higher compared with noninfected persons.⁵⁵ However, in an NHANES-based study using recent data for the diagnosis of diabetes, diabetes or IR were no longer associated with HCV infection but with alanine transferase (ALT) elevation.⁵⁶ In a large matched population-based study from Scotland, the prevalence of diabetes was low and not different between HCV-positive or HCV-negative persons.⁵⁷ The lack of

Table 2
Prevalence of hepatitis C virus infection among diabetics and controls

Author (Reference)	Study Population (n)	Diabetics (%)	Controls (%)
Mason et al, ²⁷ 1999	Diabetics (594) Thyroid (377)	4.2	1.6
Okan et al, ⁴⁰ 2002	Diabetics (692) Blood donors (1014)	7.5	0.1
Sangiorno et al, ⁴¹ 2000	Diabetics (1514)	7.6	—
Simo et al, ⁴² 1996	Diabetics (176) Blood donors (6172)	11.5	2.5

association between HCV and diabetes or IR in these population-based studies may be explained by their cross-sectional design and the rather low prevalences of HCV infection, liver disease, or diabetes. In this setting, longitudinal population-based studies have found a significant association between the risk of incident diabetes and HCV infection in most cases.^{43,44,53}

Taken together, these results suggest a direct link between HCV infection and IR, independent of BMI and visceral adiposity. They also stress the important role of HCV genotypes and high viral load in this setting.

Mechanisms of Hepatitis C Virus–Induced Insulin Resistance

Experimental and clinical studies have suggested that HCV may interact with glucose metabolism and promote IR through multiple pathogenic mechanisms: direct inhibition of insulin signaling pathway, overproduction of proinflammatory cytokines, oxidative stress, modulation of incretins, or pancreatic β -cells dysfunction.

Hepatitis C virus effects on insulin signaling pathway in the liver

A defect in postreceptor insulin signaling is involved in the HCV-induced IR. The comparison of liver biopsy of nondiabetic or nonobese chronic HCV subjects with matched noninfected controls showed a marked decrease in the ability of ionotropic receptor (IRS)-1 to associate with the insulin receptor, and a corresponding disruption of downstream signaling pathways, including reductions in insulin-stimulated tyrosine phosphorylation and phosphatidylinositol 3-kinase (PI3-K) enzymatic activity.⁵⁸ In transgenic mice, genotype 1 HCV core protein is able to suppress IRS-1 tyrosine phosphorylation leading to IR and overt diabetes.⁵⁹ Subsequent study has shown downregulation of hepatic expression of both IRS-1 and IRS-2 by the HCV core protein-mediated induction of suppressor of cytokine signaling protein (SOCS)-3 via a mechanism that involves proteosomal degradation through ubiquitination, the net result of which is compensatory increases in fasting insulin levels and hepatic IR.⁶⁰ In addition, the core protein of genotype 1 has been shown to promote IRS-1 degradation through mammalian target of rapamycin (mTOR) activation and to suppress phosphorylation of tyrosine on IRS-1, as well as the production of IRS-2, through modulation of a proteasome activator 28 γ -dependent pathway.^{61,62} The core protein of HCV genotype 3 can also promote IRS-1 degradation, and this effect is mediated by its effects on PPAR γ that lead to upregulation of SOCS-7.⁵³ HCV may also promote dephosphorylation of Akt by endoplasmic reticulum stress signal, leading to reduction of insulin signaling.⁶⁴ Interestingly, clearance of HCV infection has been shown to improve IR and restore the hepatic expression of IRS-1 and IRS-2.⁴⁹ These latter findings indicate a direct role for HCV infection in promoting IR through a reduction in insulin signaling mechanisms and a beneficial effect of anti-viral therapy on restoring insulin sensitivity in persons with HCV.

Proinflammatory cytokines and hepatitis C virus–mediated insulin resistance

Among the proinflammatory cytokines that have been associated with HCV infection in the liver, tumor necrosis factor (TNF)-alpha and its soluble receptor molecules, sTNFR1 and sTNFR2, may be most important. The levels of TNF- α in patients with CHC is strongly associated with both hepatic and systemic IR^{48,65} and the development of diabetes.⁶⁶ Levels of sTNFR1 and sTNFR2, which are considered reliable and stable indicators of TNF activation, also are significantly associated with IR, in diabetic as well in nondiabetic HCV patients.^{48,65,66} In transgenic mice, the hepatic IR caused by HCV core gene expression was principally mediated by increased TNF- α expression, whereas administration of an antibody to TNF could restore insulin levels

to normal and return insulin sensitivity to normal.⁵⁹ TNF- α can also have indirect effects on IR and adipokines in persons with HCV. In a study conducted in chronic HCV subjects, serum TNF- α levels were positively correlated with steatosis grades and HOMA-IR values, whereas serum levels of adiponectin were inversely correlated with steatosis grades, serum TNF- α levels, and HOMA-IR values.⁶⁷ These findings support the close association of TNF- α , adiponectin, steatosis, and IR in chronic HCV patients. In a study comparing proinflammatory cytokine expression in liver tissues, intrahepatic expression of the cytokine IL-18, a potent inducer of gamma-IFN, was significantly upregulated in subjects with CHC versus controls, with a concordant increase in gamma-IFN expression.⁶⁸ HCV-infected patients develop IR in peripheral tissues (mainly skeletal muscle), as well as the liver, although the molecular mechanism remains unclear.⁶⁹ In another study, CHC was even associated with peripheral, rather than hepatic, IR.⁷⁰ Although mechanisms remain unknown, humoral factors such as TNF- α might be necessary for the development of IR in peripheral tissues that are distant from the HCV-infected liver, as demonstrated in a non-HCV experimental model.⁷¹ Taken together, these data provide evidence that increased expression of TNF- α in the liver results in a suppression of insulin action in the liver and, likely, peripheral tissue, leading to IR and eventual progression to overt diabetes.

Reactive oxygen species and hepatitis C virus-mediated insulin resistance

Given the importance of reactive oxygen species (ROS) in the development of IR, it is noteworthy that HCV has been shown to be a potent inducer of ROS. In vitro and in vivo studies have demonstrated that HCV core protein was able to increase the production of ROS, without hepatic inflammation in some cases.^{72,73} In subjects with CHC, serum and hepatic levels of thioredoxin, which are markers of oxidative stress, were significantly correlated with HOMA-IR and hepatic mRNA levels independently predicted HOMA-IR.⁴⁶ Both thioredoxin level and HOMA-IR were significantly reduced after phlebotomy. These findings argue for a role of oxidative stress, which may be directly induced by HCV core protein, in the development of IR.

Incretin and hepatitis C virus-mediated insulin resistance

Few reports to date have addressed the relationship between incretin and HCV infection. One study in HCV subjects found that the level of serum incretin hormones glucagon-like peptide (GLP)-1, which promote insulin biosynthesis, insulin secretion, and β -cell survival, was significantly decreased compared with HBV or inflammatory bowel disease (IBD) subjects, or healthy controls. This decrease of GLP-1 level was associated with upregulation of liver and ileum dipeptidyl peptidase (DPP)-IV expression, which inactivate GLP-1, and with a significant decrease of hepatic glycogen content. The investigators concluded the altered expressions of GLP-1 and DPP-IV may be involved in the development of HCV-associated glucose intolerance.⁷⁴

Effect of hepatitis C virus on pancreatic β -cells

In vitro studies have demonstrated that HCV infection of human β -cells leads to a reduction in the cells' glucose-stimulated insulin release and induces apoptosis-like death through an endothelial reticulum (ER) stress-involved, caspase 3-dependent, specific pathway.^{75,76} However, in transgenic mice, the HCV core protein had no substantial effects on pancreas-related insulin, due to a compensatory increase of islet mass.⁵⁹ Further studies are needed to elucidate how HCV affects pancreatic β -cells and their production or release of insulin.

In conclusion, there is considerable evidence that HCV through its interactions with lipid metabolism promotes steatosis and hypolipidemia. The epidemiologic link between HCV and diabetes mellitus in patients with chronic liver disease rather than in

the general population suggests that inflammation play a major role in HCV-induced IR. In this setting, proinflammatory cytokines such as TNF- α have a central role, likely in liver but also in peripheral IR. Although host-related metabolic steatosis is likely involved in the promotion of IR, the role of viral-related steatosis is not evident. Therapies to reduce inflammation, HCV viral load, steatosis, and TNF- α activity can be expected to improve metabolic parameters and reduce DM risk in patients with chronic HCV.

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