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Editorial Board Member of *World Journal of Gastroenterology*, Giovanna Ferraioli, MD, FAIUM, Associate Professor, Researcher, Department of Clinical Surgical, Diagnostic and Pediatric Sciences, Medical School University of Pavia, Viale Brambilla 74, Pavia 27100, Italy. giovanna.ferraioli@unipv.it

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Metabolic complications of hepatitis C virus infection

Rahul Chaudhari, Sherouk Fouda, Ashik Sainu, Joseph M Pappachan

ORCID number: Rahul Chaudhari 0000-0002-0265-8100; Sherouk Fouda 0000-0001-8227-4571; Ashik Sainu 0000-0002-9508-2293; Joseph M Pappachan 0000-0003-0886-5255.

Author contributions: Chaudhari R and Fouda S performed extensive literature review and drafted the manuscript and share the first authorship jointly; Sainu A added points especially the hepatologic side of the work with additional literature review and revision; Pappachan JM conceived the idea, inputted additional scientific points especially the metabolic aspects, revised the entire work critically, and approved the final version for publication.

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Rahul Chaudhari, Department of Medicine, Pennsylvania Hospital of the University of Pennsylvania, Pennsylvania, PA 19104, United States

Sherouk Fouda, School of Health and Biomedical Sciences, RMIT University, Melbourne VIC 3000, Australia

Ashik Sainu, Department of Gastroenterology and Hepatology, Aster Oman Hospital, Al Ghubra, Muscat OM 133, Oman

Joseph M Pappachan, Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Preston PR2 9HT, United Kingdom

Joseph M Pappachan, Faculty of Science, Manchester Metropolitan University, Manchester M15 6BH, United Kingdom

Joseph M Pappachan, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PL, United Kingdom

Corresponding author: Joseph M Pappachan, FRCP, MD, Consultant Physician-Scientist, Honorary Research Fellow, Senior Researcher, Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Royal Preston Hospital, Preston PR2 9HT, United Kingdom. drpappachan@yahoo.co.in

Abstract

Hepatitis C virus (HCV) infection is a systemic disease that is implicated in multiple extrahepatic organ dysfunction contributing to its protean manifestations. HCV is associated with diverse extrahepatic disorders including atherosclerosis, glucose and lipid metabolic disturbances, alterations in the iron metabolic pathways, and lymphoproliferative diseases over and above the traditional liver manifestations of cirrhosis and hepatocellular carcinoma. The orchestration between HCV major proteins and the liver-muscle-adipose axis, poses a major burden on the global health of human body organs, if not adequately addressed. The close and inseparable associations between chronic HCV infection, metabolic disease, and cardiovascular disorders are specifically important considering the increasing prevalence of obesity and metabolic syndrome, and their economic burden to patients, the healthcare systems, and society. Cellular and molecular mechanisms governing the interplay of these organs and tissues in health and disease are therefore of significant interest. The coexistence of metabolic disorders and chronic hepatitis C infection also enhances the progression to liver fibrosis and hepatocellular carcinoma. The presence of metabolic disorders is believed to influence the chronicity and virulence of HCV

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leading to liver disease progression. This comprehensive review highlights current knowledge on the metabolic manifestations of hepatitis C and the potential pathways in which these metabolic changes can influence the natural history of the disease.

Key Words: Chronic hepatitis C infection; Insulin resistance; Metabolic syndrome; Cardiovascular diseases; Fatty liver; Diabetes mellitus

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Core Tip: Available evidence proves a strong association between hepatitis C virus (HCV) and metabolic complications such as hyperlipidemia, hepatic steatosis, insulin resistance, metabolic syndrome, and diabetes mellitus. *De novo* development of insulin resistance and hepatic steatosis in chronic HCV infection influences the disease progression in the liver and enhances overall morbidity and mortality. The influence of metabolic diseases on HCV infection can increase disease severity. The interplay between HCV major proteins and the liver-muscle-adipose axis is complex and still not fully elucidated. Coexistence of metabolic diseases such as diabetes mellitus and HCV infection are also known to result in adverse outcomes of both disorders. There is evidence that successful treatment halts the progression of liver disease, but more studies are required on how treatment influences the metabolic manifestations.

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INTRODUCTION

Hepatitis C virus-beyond a hepatotropic infection

Hepatitis C virus (HCV) is a major cause of liver disease worldwide, with 130-170 million people infected according to the World Health Organization^[1]. Approximately 10%-20% of chronically infected patients experience persistent inflammation and develop liver cirrhosis and eventually hepatocellular carcinoma^[1]. Well recognized extrahepatic manifestations include but not limited to; glucose and lipid metabolic disorders, atherogenic disease, mixed cryoglobulinemia, lymphoproliferative disorders, renal disease, insulin resistance (IR), type 2 diabetes (T2DM), sicca syndrome, rheumatoid arthritis-like polyarthritis, and autoimmune diseases^[2,3]. Moreover, patients with chronic HCV are at an increased risk of developing metabolic bone disease and osteopenia as it was observed in more than 50% of infected subjects^[4]. The deleterious effects of metabolic complications as a result of HCV infection is mainly due to impairments in glucose and lipid metabolism^[5]. Independent of the stage of hepatic fibrosis, IR and DM are more prevalent in the course of HCV infection and post liver transplantation in chronic HCV (CHC) infected patients^[6-8]. Interestingly, prevalence of HCV infection among diabetic patients is higher than in the age-matched general population^[9]. CHC induces systemic and hepatic inflammation that contribute to the development of atherosclerosis through elevated levels of pro-atherogenic cytokines and chemokines^[10]. Atherosclerosis is also found to be related to the high tumor necrosis factor alpha (TNF- α)/adiponectin ratio that is found in HCV-infected patients and is related to IR^[11].

The systemic burden of hepatitis C infection surpasses its liver disease burden due to its metabolic spectrum and it is plausible that, the virus, through disruptions of glucose and lipid homeostasis, stimulates other mechanisms of liver damage and contributes to the pathogenesis of extrahepatic disorders^[12]. Therefore, it is imperative to have thorough understanding on the metabolic impact of this enigmatic disease on human body for optimal management of the disease and its consequences. This evidence-based review highlights the current understanding on CHC infection and its metabolic complications.

IMPACT OF CHRONIC HEPATITIS C ON MAJOR METABOLIC ORGANS

Most HCV infected people are unaware of their condition due to its asymptomatic nature. About one-third of infections resolve spontaneously in the first year, the remaining infections persists and become chronic. CHC infection can progress to end-stage liver disease, including cirrhosis and hepatocellular carcinoma (HCC). HCV can also cause serious problems in organ systems other than the liver, including cryoglobulinemic vasculitis, metabolic bone disease, kidney disease, cardiovascular disease, and hematologic malignancies. In the United States, HCV is one of the leading causes of end-stage liver disease requiring liver transplantation, and the mortality attributed to HCV is expected to continue rising during the next 10 years. **Figure 1** illustrates the HCV-related metabolic disturbances mainly targeting the liver, skeletal muscle and adipose tissue as current evidence suggests^[13].

METABOLIC EFFECTS OF CHRONIC HEPATITIS C INFECTION ON LIVER

Hepatic steatosis in the setting of HCV viral infection is considered as a distinct entity with specific clinical and prognostic implications. The prevalence of hepatic steatosis in patients with HCV infection is 55.54%, which remains higher than that in non-infected individuals^[14]. Contrary to non-alcoholic fatty liver disease being associated with hyperlipidemia, CHC is linked with hypolipidemia including hypocholesterolemia, hypo-triglyceridemia and lower low-density lipoprotein (LDL) cholesterol levels. Co-existence of non-alcoholic fatty liver disease in HCV infected patients is associated with features of metabolic syndrome (MetS), and is an independent risk factor for advanced liver fibrosis^[15-17].

In patients with CHC, genotype 3 has the highest prevalence of hepatic steatosis (40%-86%) while patients with other genotypes is around 50%^[18,19]. A direct association exists between genotype 3 HCV (G3-HCV) and the development of steatosis, while in non-genotype 3 CHC, IR plays a key role in the pathophysiology of hepatic steatosis^[20,21].

The term “viral steatosis” is used particularly with G3-HCV infection when hepatic steatosis is related with viral load and not MetS and “metabolic steatosis” occurs secondary to IR/MetS in the genotypes G1, G2, and G4^[22-24]. Studies in patients infected with G3-HCV have demonstrated that steatosis can improve and even disappear following successful antiviral treatment with interferon and ribavirin; but data from directly acting antivirals (DAAs) are limited^[25,26]. The risk of progression of fibrosis is increased with pre-existing steatosis, and a reduced rate of response to antiviral treatment^[27-29]. CHC is implicated in the development and progression of non-alcoholic steatohepatitis (NASH). NASH is a chronic state of liver injury that can be caused by CHC infection or coexist with HCV and biopsies have proven that the association leads to advanced fibrosis and is a predictor of liver disease progression in patients with CHC regardless of the genotype^[30,31]. Both “viral” and “metabolic” steatosis, stimulates the progression of fibrosis and liver disease influenced by actions of increased insulin levels and inflammatory cytokines on hepatic stellate cells (**Figure 2**).

HEPATITIS C VIRUS AND IRON METABOLISM

Iron is a central component for HCV virus replication and translation, though it is debatable whether iron promotes or suppresses HCV viral replication. High serum ferritin levels, associated with hepatic iron overload, were evident in CHC patients and considered an independent risk factor for advanced liver fibrosis^[32,33]. Alterations of iron metabolism in CHC is believed to be caused by a reduction in the level of hepcidin. Hepcidin, a peptide hormone, is critical in the strict regulation of iron levels under homeostatic states. Though the underlying mechanisms remains unclear, the current opinion propose that all HCV proteins regulates hepcidin expression through signal transducer and activator of transcription 3, mitogen-activated protein kinase, or bone morphogenetic protein/Sma and Mad proteins signaling pathways, and the altered expression of other related genes^[34]. Due to the ability of different factors influencing the levels of serum ferritin levels, it serves as an important indicator of hepatic iron overload but only a liver biopsy can confirm the diagnosis. It is vital to further our understanding on how HCV affects iron metabolism and whether it can be used as a therapeutic tool to prevent disease progression.

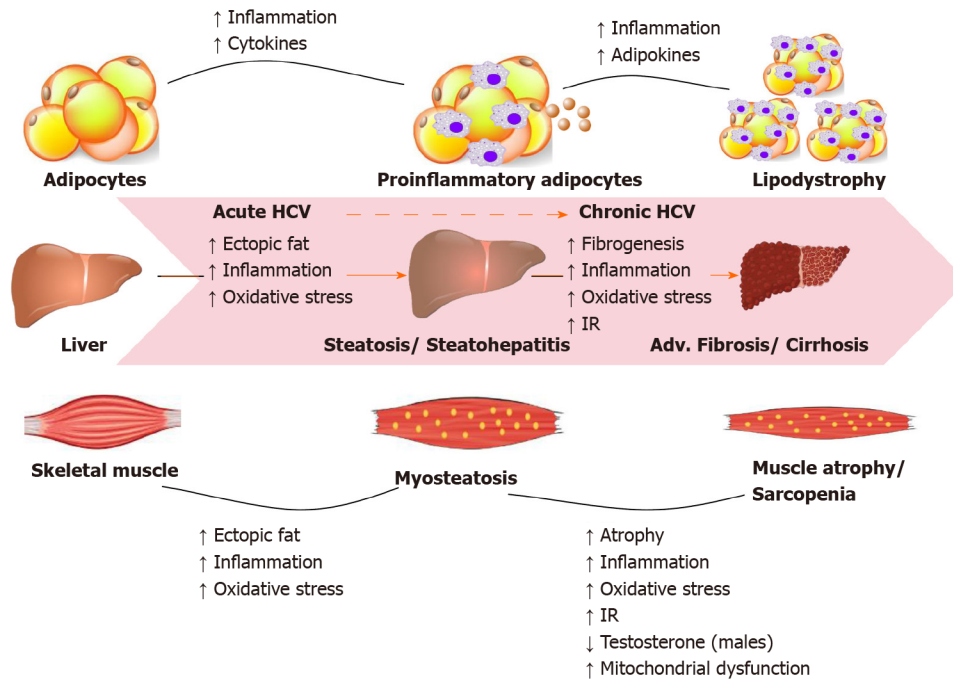


Figure 1 Changes in liver, adipose tissue, and muscle with hepatitis C virus infection. Adv: Advanced; HCV: Hepatitis C virus; IR: Insulin resistance.

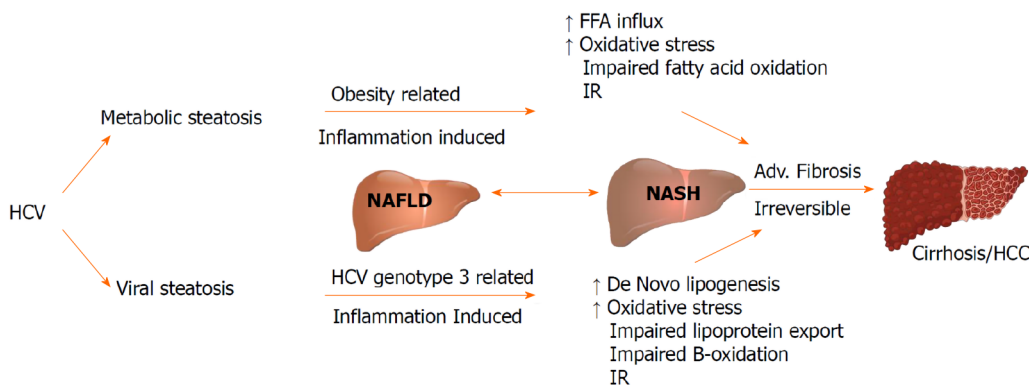


Figure 2 Hepatic steatosis development in hepatitis C virus infection. Adv: Advanced; HCV: Hepatitis C virus; NAFLD: Non-alcoholic fatty liver disease; FFA: Free fatty acid; IR: Insulin resistance; HCC: Hepatocellular carcinoma.

EFFECTS OF CHRONIC HEPATITIS C INFECTION ON SKELETAL MUSCLE

CHC infection is associated with skeletal muscle mass loss, sarcopenia, increased intramyocellular lipid deposition, myosteatosis, and low muscle strength^[35-37]. A recent Japanese study by Fukui *et al*^[38] demonstrated that skeletal muscle mass decreases in accordance with liver disease progression in male patients with CHC. Sarcopenia, loss of muscle mass and function, has a high incidence rate in patients with cirrhosis (30%-70%) favoring atrophy of type II fast-twitch glycolytic fibers^[39,40]. Myosteatosis, is characterized by increased lipid accumulation within muscle fibers and is a complication of hepatitis C Cirrhosis predisposing individuals to muscle atrophy over time^[41]. High BMI, IR, diabetes, steatosis, inflammation, increased oxidative stress and lipotoxicity are all independent risk factors that predispose CHC patients to skeletal muscle disorders^[42-47]. Therefore, a comprehensive sarcopenia evaluation assessing skeletal muscle mass, muscle strength and physical performance can provide clinicians the optimal risk assessment tools and therapeutic strategies for improving patient's quality of life and to halt the disease progression.

It is widely recognized that testosterone is highly associated with increased muscle

strength and mass^[48]. Chaudhury *et al*^[49] demonstrated that male CHC patients with hepatic dysfunction/cirrhosis suffered from low levels of free and total testosterone regardless of the treatment regimens (interferon and ribavirin (6%); interferon, ribavirin, and DAAs (18%); ribavirin and DAAs (14%); and DAAs only (62%)) received by patients^[50]. The decrease in testosterone was sustained after viral clearance suggesting that testosterone metabolism in the liver is most likely impaired by liver dysfunction in these patients. Neff *et al*^[51] was able to show that administration of testosterone hormone to HCV-patients suffering from liver failure increases muscle strength, enhance albumin synthesis, and improve survival post-liver transplant^[49,52-54].

The association between CHC infection of the liver as well as hepatic dysfunction and muscle loss is well documented, though not fully understood. The triad complex association can be linked through increased inflammation, oxidative stress, alterations in the endocrine system (IR, testosterone levels), hepatic steatosis, and multiple factors involved in muscle depletion. A better understanding of the etiology of sarcopenia and skeletal muscle mass loss in HCV infected patients and the appropriate management strategies are expected to improve patient outcomes.

HEPATITIS C VIRUS INFECTION AND ADIPOSE TISSUE

Following liver and skeletal muscles, adipose tissue is another major site of IR in CHC infections^[51]. Adipose tissue is considered as an important endocrine organ which releases biologically active polypeptides including adipose tissue specific adipokines like leptin and adiponectin and non-adipose tissue specific adipokines such as plasminogen activator inhibitor I (PAI-1)^[55]. Adiponectin (an insulin-sensitizing hormone in muscle and liver) and leptin are most abundant in subcutaneous fat while PAI-1 is found in high levels in extracellular matrix^[56,57]. Together, leptin, adiponectin and PAI-1 are the abundant adipokines which regulate the body lipid and glucose metabolism *via* the adipo-insular axis^[58]. Alterations in adipokine levels/function are a major culprit for multiple complications including the risk of developing T2DM, cardiovascular disease and neurodegenerative disorders.

An interplay between HCV virion and adipocytes is suggested by a strong relationship between HCV viral load and subcutaneous (not visceral) fat^[59]. Patients with CHC have significant subcutaneous adipose tissue insulin resistance in comparison with BMI-matched controls. Lim *et al*^[58] suggested that that viral eradication improves global, hepatic, and adipose tissue insulin sensitivity. Serum levels of adiponectin and leptins even though associated with IR, HCV associated IR is predominantly a cytokine-independent direct virus-specific effect^[60].

Though data is limited, new adipokines have an important role in the regulation of insulin sensitivity in CHC. Vaspin (visceral adipose tissue-derived serpin; seroinA12) has been found to improve insulin sensitivity and glucose tolerance and down regulate TNF- α synthesis^[61-63]. The levels of serum vaspin are significantly decreased in chronic HCV infected patients without advanced fibrosis and increased in cases of advanced fibrosis suggesting vaspin to be a compensatory mechanism switch in HCV associated IR. However, no such association was found between serum vaspin level and viral load or homeostatic model assessment of IR values^[64]. The level of another adipokine, visfatin, also increases in CHC and is inversely associated with inflammatory activity^[65]. Visfatin exerts insulin like effect stimulating insulin receptor substrate-1 (IRS-1) phosphorylation and the peroxisome proliferator-activated receptors (PPAR γ) expression but it also potentiates expression of interleukin-6 and TNF- α like adhesion molecules^[65,66]. Chimerin, another adipokine thought to be related to IR in CHC infection, inhibits the synthesis of TNF- α and interleukin-6 and ameliorates IRS-1 phosphorylation, to improve insulin sensitivity of adipocytes and to enhance adiponectin synthesis^[67,68].

HEPATITIS C VIRUS AND LIPID METABOLISM

HCV regulates the host factor diacylglycerol acyltransferase-1 to promote the biogenesis of lipid droplets, and the HCV core protein recruit nonstructural protein 5A (NS5A) that carries HCV ribonucleic acid from the replication complex on the endoplasmic reticulum-derived membranous web to lipid droplets^[69]. The enveloped viral particles may be simultaneously packaged into endoplasmic reticulum luminal lipid droplets in the very low-density lipoprotein cholesterol (VLDL) precursor and eventually the VLDL-dependent pathway secretes it into the circulation as lipo-viral

particles^[70,71]. Therefore, HCV infection is implicated in disrupted lipoprotein homeostasis due to impairment of the VLDL-releasing pathway which is one of the driving mechanisms of hepatic steatosis^[72]. Derangement of lipid metabolism in HCV infection plays a role in hepatic steatosis, dyslipidemia, and hypobetalipoproteinemia. The HCV core and NS5A proteins interact with apolipoprotein (apo) A, apo A II and apo E. An increased levels of ApoC-III has been found in HCV lipo-viral particles that may inhibit the activity of lipoprotein lipase, disturbing the intravascular catabolism of triglyceride-rich lipoproteins^[73-75]. HCV may modulate lipid metabolism and promote the synthesis of saturated fatty acids by regulating the enzymes involved in lipid synthesis^[76,77]. Poly-unsaturated fatty acids supplementation counteracts the effects of HCV-induced lipid alterations and inhibits HCV formation^[78]. Previous treatment with interferon-based antiviral therapy could reverse the hypocholesterolaemia induced by HCV. It has been shown that cholesterol and low-density lipoprotein cholesterol (LDL-C) levels rapidly recover following viral clearance or sustained virologic response indicating that large amounts of lipids released from the liver into blood circulation may increase levels of cholesterol and LDL-C, resulting in the hydrolysis of triglycerides^[79]. More studies are needed to delineate the pathways and potential therapeutic targets.

CHRONIC HEPATITIS C VIRUS AND GLUCOSE METABOLISM

CHC infection is closely associated with alterations of glucose metabolism from the early stages of infection, prior to the development of significant hepatic fibrosis^[80]. In patients infected with HCV, total serum fasting blood glucose levels are found to be higher than that in healthy controls^[81]. Clinical studies, both prospective and retrospective, showed a two-fold increased risk of developing insulin resistance and T2DM in HCV-infected patients even after correction of confounding factors^[82].

The mechanism by which HCV causes glucose metabolism derangement resulting in T2DM is not fully understood. The proposed mechanisms from experimental studies in mice suggest downregulation of glucose transporter 2 receptors causing impaired hepatic glucose uptake, down-regulation of insulin receptor substrate 2 expression [suppression of cytokine signaling (SOCS)-3-dependent mechanism] causing altered hepatic insulin receptor cascade and impaired insulin-driven hepatic neoglucogenesis switch to glycolysis, as well as a defective insulin-driven shutdown of gluconeogenesis resulting in higher endogenous glucose production. Also alterations of the forkhead box O1 phosphorylation and nuclear exclusion by HCV proteins is implicated in T2DM development^[83].

There is some evidence to suggest that HCV infected individuals are at risk of developing Type 1 diabetes mellitus through autoimmunity with some studies pointing towards pancreatic autoimmunity developing after Interferon treatment^[84]. Many epidemiologic studies have found an association between T2DM and HCV infection possibly due to an interplay of multiple factors including direct viral effects, cytokine milieu, IR *etc.*^[85] T2DM can accelerate the natural course of HCV-induced liver disease causing higher risk of fibrosis, cirrhosis, and hepatocellular carcinoma^[86]. In patients with CHC infection and T2DM, significant improvement was noted in their diabetes status after HCV eradication with treatment^[87-90]. The patients who did not achieve sustained virological response had a higher risk of T2DM^[91-96]. **Figure 3** illustrates the deleterious effects of HCV on glucose and lipid metabolism.

HEPATITIS C VIRUS AND INSULIN RESISTANCE: CENTRAL AND PERIPHERAL PATHWAYS

HCV proteins that are mainly involved in IR include core proteins, Serine protease and nonstructural viral proteins NS5A and NS5B that contribute to the formation of capsid, down-regulation of interferon-stimulated genes and polymerase activity. HCV induces IR both through multiple pathways and appears to depend on viral load and specifically genotypes G 1, 2 and 4^[97].

In the direct mechanism, HCV proteins interact with various components of the insulin signaling pathway disrupting the signaling process of insulin in the hepatocytes. This leads to overexpression of protein phosphatase 2A and SOCS-3, and down regulates the expression of PPAR and IRS causing IR directly. HCV infection enhances hepatic gluconeogenesis through forkhead box O1-dependent pathway and

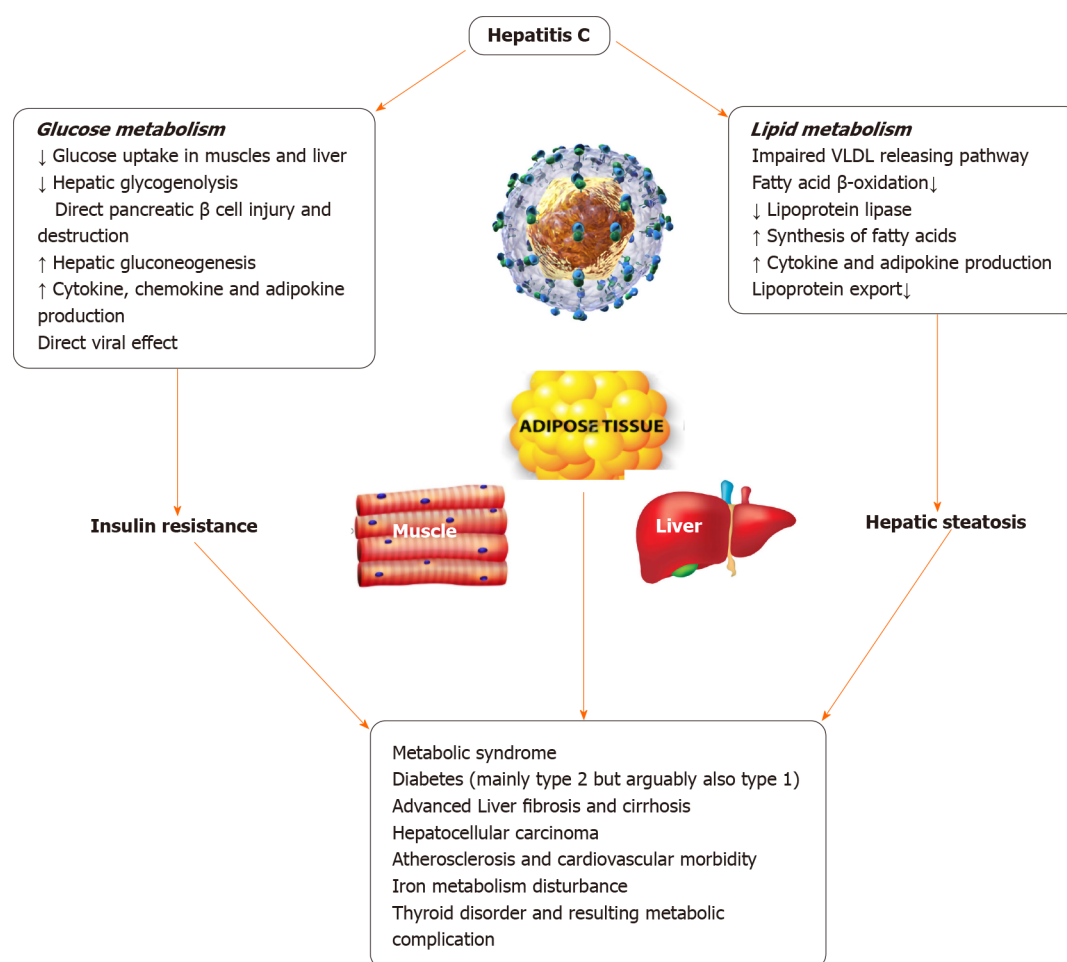


Figure 3 Impact of hepatitis C virus on glucose and lipid metabolism.

suppresses the cell surface expression of glucose transporter 2, resulting in reduced glucose uptake with the help of HCV NS5A protein that plays important roles in these two independent pathways. Any disruption in insulin signaling results in various pathophysiological changes, including glucose intolerance, obesity, dyslipidemia, hypertension, and development of T2DM^[98-100]. The mechanism of insulin impairment appears HCV genotype specific, as core protein expression of G3 led to upregulation of SOCS-7 and downregulation of PPAR γ , while the core protein from G1 activated mammalian target of rapamycin and induced phosphorylation of IRS-1 at inhibitory serine residues^[101]. However, activation of SOCS family appeared to be common mechanism for all major genotypes to induce IR, including genotype 1 as the mammalian target of rapamycin activating variant appeared to be infrequent among known isolates^[102-107].

Peripheral IR is the deficits in insulin induced glucose uptake into target tissues (adipose and muscle tissues). IR in CHC infection is thought to primarily affect muscle tissue making it a notable paradigm of IR. Mangia *et al*^[106] showed that peripheral insulin resistance and resulting T2DM does not develop for at least first 5 years of infection with HCV suggesting the role of chronic infection in the development of IR rather than acute infection^[107]. The pathways of lipid metabolism derangements and IR induced by HCV proteins and host cells opens up potential future treatment options scope for more studies^[107,108].

The main PPAR nuclear receptors expressed in the liver that regulates glucose and lipid metabolism, influence cellular differentiation and proliferation as well as regulate the inflammatory process, include PPAR α and PPAR γ alongside retinoid X receptor. PPAR α gene expression in the liver is decreased by 86% in the course of CHC infection^[109]. Studies demonstrated a sharp decrease in the hepatic PPAR γ expression in G3 CHC patients compared to those with G1 HCV^[109-114].

The major pathways by which CHC infection induce insulin resistance are shown in the Table 1.

Table 1 The role of major hepatitis C virus proteins in insulin resistance development

HCV core protein	Nonstructural protein 3 (NS3)	Nonstructural protein 5 (NS5)
Activates members of SOCS family; Genotype 1: Activates mTOR and induces phosphorylation of IRS-1; Genotype 3: Upregulates SOCS-7 and downregulates PPAR γ	NOX2 activation	Increasing the ROS within the mitochondria
↓ PPAR α gene expression in the liver	↑ ROS	Induces ER stress → ↑ protein phosphatase 2A (PP2A)
↓ Assembly of VLDL	Through ROS → Activation of transcriptional factors such as NF- κ B and STAT-3 → more advanced stages of chronic hepatitis → oncogenesis	Dephosphorylation and inactivation of Akt
Induces lipogenesis and gluconeogenesis		Stimulates the NF- κ B-mediated increase in proinflammatory cytokines
↓ IFN- α production; ↓ IFN- α stimulated genes		Up-regulation of PP2Ac → hypomethylation of STAT-1 → ↑ association of STAT-1 with PIAS1PIAS1 → impairing the transcriptional activation of IFN-stimulated genes
Activation of the pattern-recognition receptor TLR2 → ↑ production of profibrotic factors. <i>i.e.</i> TGF- β , procollagen 1, and MMPs		Stimulates the NF- κ B → increase in proinflammatory cytokines (<i>i.e.</i> IL-6, TNF- α)
Activates the PA28 γ → ↓ IRS-1 tyrosine phosphorylation and IRS-2 expression and TNF- α promoter activation		Dephosphorylation of PKB/Akt → inhibition of insulin signaling
Induces TNF α → portal or periportal inflammation		
Impedes insulin-mediated FoxO1 translocation affecting glucose metabolism		

Akt: Protein kinase B; PKB: Protein kinase B; ER: Endoplasmic reticulum; FoxO1: Forkhead box protein O1; IFN- α : Interferon alpha; IL-6: Interleukin-6; IRS-1: Insulin receptor substrate 1; IRS-2: Insulin receptor substrate 2; MMPs: Matrix metalloproteinases; mTOR: Mammalian target of rapamycin; NF- κ B: Nuclear factor kappa light chain; NOX2: NADPH oxidase 2; NS3: Serine protease; NS5: Nonstructural viral proteins NS5A and NS5B; PA28 γ : Proteasomal activator; PIAS1: Protein inhibitor of activated STAT 1; PP2Ac: Catalytic subunit of protein phosphatase 2A; ROS: Reactive oxygen species; SOCS: Suppressors of cytokine signaling; SOCS-7: Suppressor Of cytokine signaling 7; STAT-1: Signal transducer and activator of transcription 1; TGF- β : Transforming growth factor beta; TNF- α : Tumor necrosis factor α ; TLR2: Toll-like receptor 2; VLDL: Very low density lipoprotein.

HEPATITIS C VIRUS AND METABOLIC SYNDROME

According to the Joint Scientific Statement in 2009, patients who exhibit three of the five following characteristics are diagnosed with the metabolic syndrome (MetS): (1) Abnormal waist circumference as population and country-specific definitions; (2) Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or currently taking blood pressure-lowering agents; (3) High-density lipoprotein of cholesterol < 40 mg/dL in males or < 50 mg/dL in females; (4) Fasting blood sugar ≥ 100 mg/dL or currently taking diabetes medications; and (5) Triglyceride ≥ 150 mg/dL^[115,116]. Both CHC infection and the MetS have common basic pathogenesis which is glucose metabolic derangement and IR resulting in close association and overlapping manifestations^[117]. Amongst HCV infected patients, particularly older subjects, the prevalence of MetS ranges from 13.2% to 31.5%^[118]. The prevalence increases in patients with CHC, older than 60 years of age, having an odds ratio of eight times of developing MetS than those under 40 years of age. A study by Lonardo *et al*^[118] exploring the association between HCV genotypes and MetS prevalence found no significant difference compared to controls^[119]. This could be due to the small sample size and patient selection criteria.

More studies show that African Americans infected with HCV are more prone to develop MetS than other ethnic groups^[120,121]. An aggressive and severe liver disease is common in CHC patients with MetS. Liver fibrosis is notably more advanced in CHC patients with MetS than those without^[122]. The prevalence of liver cirrhosis in CHC-MetS patients was 30% compared to 18.4% in CHC patients without MetS^[123,124]. As MetS may worsen the progression of liver diseases in HCV infected patients, further research is needed to assess the impact of viral clearance and sustained virologic response on MetS.

IMPACT OF METABOLIC DISEASE ON CHRONIC HEPATITIS C DISEASE PROGRESSION

It is crucial to understand the impact of underlying metabolic diseases on the natural history of CHC infection as much as to understand the risk of developing metabolic complications from CHC. Given the rising prevalence of obesity and metabolic syndrome observed in the United States and globally, recognition of the impact of obesity and IR in disease progression among patients with CHC is particularly important^[125].

In a recent systemic review by Dyal *et al*^[124] 20 cohort studies were identified to evaluate the impact of metabolic diseases on disease progression among patients with CHC^[125]. The authors evaluated the effect of obesity, diabetes, and steatosis as risk factors for developing advanced fibrosis in patients with chronic HCV infection and demonstrated that the presence of concurrent diabetes among patients with CHC infection was associated with a significantly higher risk of developing advanced fibrosis, with effect measures ranging from odds ratios of 2.25 to 9.24. Hepatic steatosis was also strongly associated with an increased risk of developing advanced fibrosis, with odds ratios of 1.80 to 14.3^[126]. However, further studies are needed to assess the association between obesity and advanced fibrosis in CHC patients.

Available evidence aimed to better clarify the impact of concurrent metabolic diseases on disease progression and the natural history of chronic HCV infection; however, several limitations while interpreting the results must be acknowledged. The standard method for exploring the effects of metabolic diseases on disease progression would be to recognize patients with pre-existing metabolic diseases who eventually acquired HCV infection. However, a number of these studies were observational in nature and either utilized a case-control or retrospective cohort study design, which inherently limit the true ability to understand causal links. Significant advancements in HCV therapy were introduced subsequent to these studies which may influence the metabolic milieu and disease progression differently and we need more evidence before we extrapolate the current data to the presently available regimens.

The presence of metabolic diseases may influence the sequela of HCV infection. Patients with diabetes, hepatic steatosis, NASH, and insulin resistance were at more risk of developing CHC compared to patients without underlying metabolic disorders^[127,128]. These patients were also found to have a faster progression to liver fibrosis through the same mediators that are inducing inflammation. A study by Paradis *et al*^[129] investigated the risk of developing HCC in patients with underlying metabolic syndrome disorders and found there is a profound role of MetS in HCC development and progression. This can be further aggravated by the presence of HCV. The presence of NASH is a major contributor to liver cirrhosis in the presence/absence of HCV^[130,131]. These findings elucidate the strong association between MetS disorders, HCV and their complex involvement in liver disease progression. This evidence contributes to a shift in HCC etiology which signifies further research.

MANAGEMENT OF METABOLIC COMPLICATIONS IN CHRONIC HEPATITIS C

Advances in treatment options with highly effective DAAs therapy for CHC aimed for eradication of HCV will not only improve HCV-related liver disease but will most likely impact the incidence and prevalence of HCV-related metabolic diseases, given the strong association between the two conditions. The efficacy of current regimens for CHC has improved the sustained virologic response reaching almost > 95%-100%. It is important to know whether the patient is treatment naïve or experienced, the genotype, the fibrosis level, and underlying comorbidities for personalized medicine and best tailored treatment options.

Concurrent management of coexistent metabolic disorders is also important for optimal control of CHC related liver injury and complications such as HCC as mentioned earlier. However, a detailed discussion of management of these conditions is beyond the scope of this review.

CONCLUSION

Hepatitis C infection has emerged as a systemic infection with impacts beyond the primary site of infection, causing a wide range of clinical manifestations in patients. It is crucial to understand the systemic effects of CHC along with its hepatic complications as it relates to metabolic manifestations and complications. HCV virion exploits the multiple functions of lipid droplets to sustain its multiplication and replication within host cells. The orchestration between HCV major proteins and the liver-muscle-adipose axis, poses a major burden on all the health systems of human body if not adequately addressed. The close and inseparable associations between chronic HCV infection, metabolic disease, and cardiovascular disorders are specifically important considering the increasing prevalence of obesity and metabolic syndrome and their economic burden to patients, the healthcare systems, and society. Cellular and molecular mechanisms governing the interplay of these three organs in health and disease are therefore of significant interest. As indicated by the extent of the metabolic comorbidities discussed, HCV increases the disruption in the liver-muscle-adipose triangle resulting in myriad clinical outcomes in patients. Further studies are needed to assess the association between metabolic derangement and patient quality of life. Physicians are encouraged to pay close attention to the metabolic parameters in HCV patients especially cirrhotics and patients listed for liver transplant.

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