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**Metabolic aspects of hepatitis C virus**

El-Kassas M *et al*. Metabolic aspects of HCV

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**Abstract**

Many metabolic factors are associated with chronic hepatitis C virus (HCV) 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 chronic HCV (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 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. 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 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:** Hepatitis C virus (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[2-4]. Different metabolic aspects of HCV are demonstrated in Figure 1. There are several studies on the effect of metabolic factors on the natural history of patients with chronic HCV (CHC)[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, CHC 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 CHC 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 CHC patients and impact the results of antiviral treatments[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[8,9].Interestingly, this is not a “one-way street,” as CHC 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 sequelae[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[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 CHC infection on metabolic features.

**IR**

IR is considered a keystone of metabolic syndrome (MS) with increasing incidence worldwide, representing a major cause of morbidity and mortality[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[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[1]. Moreover, CHC is found to increase the risk of developing metabolic diseases with these complications[16]. IR in patients with CHC significantly impacts the severity and progression of chronic liver disease *via* direct and indirect effects by inducing steatosis[17]. Meanwhile, steatosis activates stellate cells *via* collagenous deposition and the generation of lipid peroxides[18], which, in turn, promotes fibrogenesis *via* the direct activation of hepatic stellate cells, tumor necrosis factor-α and connective growth factor production, and ductular reactions induction[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 IR, not only in interferon-based treatment[7].

Moreover, there is a reported association between IR and the presence of esophageal varices in patients with HCV-related compensated cirrhosis[20]. The potential of insulin to control dynamic components of portal hypertension, such as endothelial nitric oxide and endothelin production, might explain this[21,22]. 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[23-25]. 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[26]. Several studies have reported the impact of IR and steatosis and both rapid virological response and 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[27]. 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 direct-acting antivirals (DAAs) to eliminate HCV improves their glycemic control with a possible reduction on the faster progression of hepatic fibrosis[28,29].

Also, treatment of HCV with DAAs found to improve steatosis, hepatic inflammation, and the nutritional status in most of the studied patients[30-32].

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 DM2[33,34].

**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[35,36]. 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[5]. 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[37]. Interestingly, steatosis has also been related to HCV viral load and was found to decrease after SVR was achieved[35]. 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[10,38]. 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[39,40].

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[41,42]. In this clinical setting, many studies reported the association between steatosis in fatty liver and HCC development in patients with CHC[43].

**Visceral Obesity**

In the context of steatosis and IR, visceral obesity has been associated with liver fat accumulation in healthy subjects[44,45] and is also related to viral load. Several studies have discussed the association between HCV RNA status and obesity[46].

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[47].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 (LDLs)-releasing pathway, which is one of the main causes of hepatic fat deposition[48]. Several studies have discussed the relationship between lipoproteins and HCV cell cycle[49] and found that patients with CHC have lower serum LDL[50], which are inversely associated with the severity of liver fibrosis[51]; however, this is still a controversial issue. As reported by Nevola *et al*[15], the average LDL levels increased significantly after viral eradication, although there were no effects on triglycerides and high-density lipoprotein[15]. 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[52]. 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[7].

HCV infection could be an independent risk factor for increased carotid IMT[53] and cerebrovascular deaths[54], 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[7]. 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[55]. Therefore, further studies are needed to validate those data.

**The role of Vitamin D**

Of 25-Hydroxyvitamin D deficiency has been discovered in patients with CHC, even in those with minimal liver damage[56]; however, some studies reported no association between vitamin D status and fibrosis stage[57]. 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[58-60].

**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[10]. 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[61,62]. 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[10,63].

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[10].

**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[64,65]. 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[66,67]. The association between CHC infection of the liver and muscle loss is well documented[68,69].High body mass index, 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[70-73].

**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[74,75].Another report stated that long-term hormonal replacement therapy could prevent accelerated liver fibrosis in menopausal women with CHC[76]. Noteworthy improvement in sexual dysfunction was reported in males and females after HCV treatment with direct-acting antivirals[77].

**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.

**REFERENCES**

1 **Lavanchy D**. The global burden of hepatitis C. *Liver Int* 2009; **29 Suppl 1:** 74-81 [PMID: 19207969 DOI: 10.1111/j.1478-3231.2008.01934.x]

2 **Qasim SF**, Jami A, Imran P, Mushtaque R, Khan RN. Frequency of Metabolic Syndrome in Chronic Hepatitis C Patients: Findings From a Lower Middle Income Country. *Cureus* 2020; **12**: e11975 [PMID: 33425547 DOI: 10.7759/cureus.11975]

3 **Fabrizi F**, Donato FM, Messa P. Hepatitis C and Its Metabolic Complications in Kidney Disease. *Ann Hepatol* 2017; **16**: 851-861 [PMID: 29055921 DOI: 10.5604/01.3001.0010.5275]

4 **Younossi Z**, Park H, Henry L, Adeyemi A, Stepanova M. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. *Gastroenterology* 2016; **150**: 1599-1608 [PMID: 26924097 DOI: 10.1053/j.gastro.2016.02.039]

5 **Macaluso FS**, Maida M, Minissale MG, Li Vigni T, Attardo S, Orlando E, Petta S. Metabolic factors and chronic hepatitis C: a complex interplay. *Biomed Res Int* 2013; **2013**: 564645 [PMID: 23956991 DOI: 10.1155/2013/564645]

6 **Chang ML**. Metabolic alterations and hepatitis C: From bench to bedside. *World J Gastroenterol* 2016; **22**: 1461-1476 [PMID: 26819514 DOI: 10.3748/wjg.v22.i4.1461]

7 **Petta S**. Insulin resistance and diabetes mellitus in patients with chronic hepatitis C: spectators or actors? *Dig Liver Dis* 2012; **44**: 359-360 [PMID: 22418268 DOI: 10.1016/j.dld.2012.02.001]

8 **Esmat G**, El Kassas M, Hassany M, Gamil M, El Raziky M. Optimizing treatment for HCV genotype 4: PEG-IFN alfa 2a vs. PEG-IFN alfa 2b; the debate continues. *Liver Int* 2014; **34 Suppl 1**: 24-28 [PMID: 24373075 DOI: 10.1111/liv.12397]

9 **El Kassas M**, Elbaz T, Hafez E, Esmat G. Safety of direct antiviral agents in the management of hepatitis C. *Expert Opin Drug Saf* 2016; **15**: 1643-1652 [PMID: 27661100 DOI: 10.1080/14740338.2017.1240781]

10 **Bugianesi E**, Salamone F, Negro F. The interaction of metabolic factors with HCV infection: does it matter? *J Hepatol* 2012; **56 Suppl 1**: S56-S65 [PMID: 22300466 DOI: 10.1016/S0168-8278(12)60007-5]

11 **Deltenre P**, Louvet A, Lemoine M, Mourad A, Fartoux L, Moreno C, Henrion J, Mathurin P, Serfaty L. Impact of insulin resistance on sustained response in HCV patients treated with pegylated interferon and ribavirin: a meta-analysis. *J Hepatol* 2011; **55**: 1187-1194 [PMID: 21703195 DOI: 10.1016/j.jhep.2011.03.010]

12 **Chaudhari R**, Fouda S, Sainu A, Pappachan JM. Metabolic complications of hepatitis C virus infection. *World J Gastroenterol* 2021; **27**: 1267-1282 [PMID: 33833481 DOI: 10.3748/wjg.v27.i13.1267]

13 **Ziolkowska S**, Binienda A, Jabłkowski M, Szemraj J, Czarny P. The Interplay between Insulin Resistance, Inflammation, Oxidative Stress, Base Excision Repair and Metabolic Syndrome in Nonalcoholic Fatty Liver Disease. *Int J Mol Sci* 2021; **22** [PMID: 34681787 DOI: 10.3390/ijms222011128]

14 **Adinolfi LE**, Jacobson I, Bondin M, Cacoub P. Expert opinion on managing chronic HCV infection in patients with type 2 diabetes mellitus. *Antivir Ther* 2018; **23**: 11-21 [PMID: 30451154 DOI: 10.3851/IMP3255]

15 **Nevola R**, Rinaldi L, Zeni L, Sasso FC, Pafundi PC, Guerrera B, Marrone A, Giordano M, Adinolfi LE. Metabolic and renal changes in patients with chronic hepatitis C infection after hepatitis C virus clearance by direct-acting antivirals. *JGH Open* 2020; **4**: 713-721 [PMID: 32782961 DOI: 10.1002/jgh3.12324]

16 **Kierepa A**, Witkowska A, Kaczmarek M, Książek K, Mikuła-Pietrasik J, Żeromski J, Kowala-Piaskowska A, Mozer-Lisewska I. Impact of chronic HCV treatment on quality of life of patients with metabolic disorders in context of immunological disturbances. *Sci Rep* 2020; **10**: 10388 [PMID: 32587314 DOI: 10.1038/s41598-020-67296-9]

17 **Stepanova M**, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. *Gut* 2010; **59**: 1410-1415 [PMID: 20660697 DOI: 10.1136/gut.2010.213553]

18 **Browning JD**, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest* 2004; **114**: 147-152 [PMID: 15254578 DOI: 10.1172/JCI22422]

19 **Bridle KR**, Li L, O'Neill R, Britton RS, Bacon BR. Coordinate activation of intracellular signaling pathways by insulin-like growth factor-1 and platelet-derived growth factor in rat hepatic stellate cells. *J Lab Clin Med* 2006; **147**: 234-241 [PMID: 16697771 DOI: 10.1016/j.lab.2005.12.009]

20 **Wang XX**, Song ZZ. Insulin resistance is a risk factor for esophageal varices in hepatitis C virus cirrhosis. *Hepatology* 2009; **49**: 1775; author reply 1776 [PMID: 19402107 DOI: 10.1002/hep.22892]

21 **Vincent MA**, Montagnani M, Quon MJ. Molecular and physiologic actions of insulin related to production of nitric oxide in vascular endothelium. *Curr Diab Rep* 2003; **3**: 279-288 [PMID: 12866989 DOI: 10.1007/s11892-003-0018-9]

22 **Iwakiri Y**, Groszmann RJ. Vascular endothelial dysfunction in cirrhosis. *J Hepatol* 2007; **46**: 927-934 [PMID: 17391799 DOI: 10.1016/j.jhep.2007.02.006]

23 **Zimmet P**. The burden of type 2 diabetes: are we doing enough? *Diabetes Metab* 2003; **29**: 6S9-618 [PMID: 14502096 DOI: 10.1016/s1262-3636(03)72783-9]

24 **Wang CS**, Wang ST, Yao WJ, Chang TT, Chou P. Hepatitis C virus infection and the development of type 2 diabetes in a community-based longitudinal study. *Am J Epidemiol* 2007; **166**: 196-203 [PMID: 17496314 DOI: 10.1093/aje/kwm061]

25 **Algarem N**, Sholkamy A, Alshazly M, Daoud A. New-onset diabetes and hypertension as complications of liver transplantation. *Transplant Proc* 2014; **46**: 870-872 [PMID: 24767368 DOI: 10.1016/j.transproceed.2013.12.007]

26 **Petta S**, Craxì A. Hepatocellular carcinoma and non-alcoholic fatty liver disease: from a clinical to a molecular association. *Curr Pharm Des* 2010; **16**: 741-752 [PMID: 20388084 DOI: 10.2174/138161210790883787]

27 **Petta S**, Rosso C, Leung R, Abate ML, Booth D, Salomone F, Gambino R, Rizzetto M, Caviglia P, Smedile A, Grimaudo S, Cammà C, Craxì A, George J, Bugianesi E. Effects of IL28B rs12979860 CC genotype on metabolic profile and sustained virologic response in patients with genotype 1 chronic hepatitis C. *Clin Gastroenterol Hepatol* 2013; **11**: 311-7.e1 [PMID: 23220171 DOI: 10.1016/j.cgh.2012.11.022]

28 **Adinolfi LE**, Rinaldi L, Marrone A, Giordano M. The effect of sustained virological response by direct-acting antivirals on insulin resistance and diabetes mellitus in patients with chronic hepatitis C. *Expert Rev Anti Infect Ther* 2018; **16**: 595-597 [PMID: 30047799 DOI: 10.1080/14787210.2018.1505500]

29 **Gualerzi A**, Bellan M, Smirne C, Tran Minh M, Rigamonti C, Burlone ME, Bonometti R, Bianco S, Re A, Favretto S, Bellomo G, Minisini R, Carnevale Schianca GP, Pirisi M. Improvement of insulin sensitivity in diabetic and non diabetic patients with chronic hepatitis C treated with direct antiviral agents. *PLoS One* 2018; **13**: e0209216 [PMID: 30571711 DOI: 10.1371/journal.pone.0209216]

30 **Saldarriaga OA**, Dye B, Pham J, Wanninger TG, Millian D, Kueht M, Freiberg B, Utay N, Stevenson HL. Comparison of liver biopsies before and after direct-acting antiviral therapy for hepatitis C and correlation with clinical outcome. *Sci Rep* 2021; **11**: 14506 [PMID: 34267267 DOI: 10.1038/s41598-021-93881-7]

31 **Shimada M,** Iwase H, Hirashima N, Ryuge N, Urata N. Nutritional status and liver steatosis after direct-acting antiviral treatment for chronic hepatitis C virus infection. *J Transl Sci* 2017; 3 [DOI: 10.15761/jts.1000194]

32 **Kawagishi N**, Suda G, Nakamura A, Kimura M, Maehara O, Suzuki K, Nakamura A, Ohara M, Izumi T, Umemura M, Nakai M, Sho T, Natsuizaka M, Morikawa K, Ogawa K, Kudo Y, Nishida M, Miyoshi H, Sakamoto N. Liver steatosis and dyslipidemia after HCV eradication by direct acting antiviral agents are synergistic risks of atherosclerosis. *PLoS One* 2018; **13**: e0209615 [PMID: 30576386 DOI: 10.1371/journal.pone.0209615]

33 **Ciancio A**, Bosio R, Bo S, Pellegrini M, Sacco M, Vogliotti E, Fassio G, Bianco Mauthe Degerfeld AGF, Gallo M, Giordanino C, Terzi di Bergamo L, Ribaldone D, Bugianesi E, Smedile A, Rizzetto M, Saracco GM. Significant improvement of glycemic control in diabetic patients with HCV infection responding to direct-acting antiviral agents. *J Med Virol* 2018; **90**: 320-327 [PMID: 28960353 DOI: 10.1002/jmv.24954]

34 **Estefan S**, Brandão-Melo CE, Dos Santos Silva CM, Gomes DCK, Cardoso P, Costa MHS. Metabolic Evaluation in Patients With Hepatitis C Treated With Direct Antiviral Agents. *Front Med (Lausanne)* 2021; **8**: 631600 [PMID: 34136497 DOI: 10.3389/fmed.2021.631600]

35 **Adinolfi LE**, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; **33**: 1358-1364 [PMID: 11391523 DOI: 10.1053/jhep.2001.24432]

36 **Lonardo A**, Loria P, Adinolfi LE, Carulli N, Ruggiero G. Hepatitis C and steatosis: a reappraisal. *J Viral Hepat* 2006; **13**: 73-80 [PMID: 16436124 DOI: 10.1111/j.1365-2893.2005.00669.x]

37 **Negro F**. Mechanisms and significance of liver steatosis in hepatitis C virus infection. *World J Gastroenterol* 2006; **12**: 6756-6765 [PMID: 17106922 DOI: 10.3748/wjg.v12.i42.6756]

38 **Castéra L**, Hézode C, Roudot-Thoraval F, Bastie A, Zafrani ES, Pawlotsky JM, Dhumeaux D. Worsening of steatosis is an independent factor of fibrosis progression in untreated patients with chronic hepatitis C and paired liver biopsies. *Gut* 2003; **52**: 288-292 [PMID: 12524415 DOI: 10.1136/gut.52.2.288]

39 **Mihm S**. Hepatitis C virus, diabetes and steatosis: clinical evidence in favor of a linkage and role of genotypes. *Dig Dis* 2010; **28**: 280-284 [PMID: 20460924 DOI: 10.1159/000282103]

40 **Esmat G**, El Akel W, Metwally M, Soliman A, Doss W, Hamid MA, Kamal M, Zalata K, Khattab H, El-Kassas M, Esmat M, Hasan A, El-Raziky M. Improvement of steatosis after interferon therapy in HCV genotype 4 is related to weight loss. *Indian J Gastroenterol* 2009; **28**: 45-48 [PMID: 19696987 DOI: 10.1007/s12664-009-0016-1]

41 **Persico M**, Iolascon A. Steatosis as a co-factor in chronic liver diseases. *World J Gastroenterol* 2010; **16**: 1171-1176 [PMID: 20222159 DOI: 10.3748/wjg.v16.i10.1171]

42 **Younossi ZM**, Stepanova M, Nader F, Younossi Z, Elsheikh E. Associations of chronic hepatitis C with metabolic and cardiac outcomes. *Aliment Pharmacol Ther* 2013; **37**: 647-652 [PMID: 23384408 DOI: 10.1111/apt.12234]

43 **Pekow JR**, Bhan AK, Zheng H, Chung RT. Hepatic steatosis is associated with increased frequency of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis. *Cancer* 2007; **109**: 2490-2496 [PMID: 17487861 DOI: 10.1002/cncr.22701]

44 **González-Reimers E**, Castellano-Higuera A, Alemán-Valls R, Alvarez-Argüelles H, de la Vega-Prieto MJ, Abreu-González P, López-Prieto J, Santolaria-Fernández F, Valladares-Parrilla F. Relation between body fat and liver fat accumulation and cytokine pattern in non-alcoholic patients with chronic HCV infection. *Ann Nutr Metab* 2009; **55**: 351-357 [PMID: 19851063 DOI: 10.1159/000252351]

45 **Leandro G**, Mangia A, Hui J, Fabris P, Rubbia-Brandt L, Colloredo G, Adinolfi LE, Asselah T, Jonsson JR, Smedile A, Terrault N, Pazienza V, Giordani MT, Giostra E, Sonzogni A, Ruggiero G, Marcellin P, Powell EE, George J, Negro F; HCV Meta-Analysis (on) Individual Patients' Data Study Group. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology* 2006; **130**: 1636-1642 [PMID: 16697727 DOI: 10.1053/j.gastro.2006.03.014]

46 **Chen W**, Wong T, Tomlinson G, Krahn M, Heathcote EJ. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. *J Hepatol* 2008; **49**: 711-717 [PMID: 18619698 DOI: 10.1016/j.jhep.2008.05.013]

47 **Everhart JE**, Lok AS, Kim HY, Morgan TR, Lindsay KL, Chung RT, Bonkovsky HL, Ghany MG; HALT-C Trial Group. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. *Gastroenterology* 2009; **137**: 549-557 [PMID: 19445938 DOI: 10.1053/j.gastro.2009.05.007]

48 **Yoshimura T**, Oppenheim JJ. Chemerin reveals its chimeric nature. *J Exp Med* 2008; **205**: 2187-2190 [PMID: 18809717 DOI: 10.1084/jem.20081736]

49 **André P**, Perlemuter G, Budkowska A, Bréchot C, Lotteau V. Hepatitis C virus particles and lipoprotein metabolism. *Semin Liver Dis* 2005; **25**: 93-104 [PMID: 15732001 DOI: 10.1055/s-2005-864785]

50 **Kanda T**, Moriyama M. Direct-acting antiviral agents against hepatitis C virus and lipid metabolism. *World J Gastroenterol* 2017; **23**: 5645-5649 [PMID: 28883690 DOI: 10.3748/wjg.v23.i31.5645]

51 **Lange CM**, von Wagner M, Bojunga J, Berg T, Farnik H, Hassler A, Sarrazin C, Herrmann E, Zeuzem S. Serum lipids in European chronic HCV genotype 1 patients during and after treatment with pegylated interferon-α-2a and ribavirin. *Eur J Gastroenterol Hepatol* 2010; **22**: 1303-1307 [PMID: 20729742 DOI: 10.1097/MEG.0b013e32833de92c]

52 **Butt AA**, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis* 2009; **49**: 225-232 [PMID: 19508169 DOI: 10.1086/599371]

53 **Marzouk D**, Sass J, Bakr I, El Hosseiny M, Abdel-Hamid M, Rekacewicz C, Chaturvedi N, Mohamed MK, Fontanet A. Metabolic and cardiovascular risk profiles and hepatitis C virus infection in rural Egypt. *Gut* 2007; **56**: 1105-1110 [PMID: 16956918 DOI: 10.1136/gut.2006.091983]

54 **Lee MH**, Yang HI, Wang CH, Jen CL, Yeh SH, Liu CJ, You SL, Chen WJ, Chen CJ. Hepatitis C virus infection and increased risk of cerebrovascular disease. *Stroke* 2010; **41**: 2894-2900 [PMID: 20966408 DOI: 10.1161/STROKEAHA.110.598136]

55 **Miyajima I**, Kawaguchi T, Fukami A, Nagao Y, Adachi H, Sasaki S, Imaizumi T, Sata M. Chronic HCV infection was associated with severe insulin resistance and mild atherosclerosis: a population-based study in an HCV hyperendemic area. *J Gastroenterol* 2013; **48**: 93-100 [PMID: 22678465 DOI: 10.1007/s00535-012-0610-3]

56 **Petta S**, Grimaudo S, Marco VD, Scazzone C, Macaluso FS, Cammà C, Cabibi D, Pipitone R, Craxì A. Association of vitamin D serum levels and its common genetic determinants, with severity of liver fibrosis in genotype 1 chronic hepatitis C patients. *J Viral Hepat* 2013; **20**: 486-493 [PMID: 23730842 DOI: 10.1111/jvh.12072]

57 **Esmat G**, El Raziky M, Elsharkawy A, Sabry D, Hassany M, Ahmed A, Assem N, El Kassas M, Doss W. Impact of vitamin D supplementation on sustained virological response in chronic hepatitis C genotype 4 patients treated by pegylated interferon/ribavirin. *J Interferon Cytokine Res* 2015; **35**: 49-54 [PMID: 25061714 DOI: 10.1089/jir.2014.0060]

58 **Kitson MT**, Dore GJ, George J, Button P, McCaughan GW, Crawford DH, Sievert W, Weltman MD, Cheng WS, Roberts SK. Vitamin D status does not predict sustained virologic response or fibrosis stage in chronic hepatitis C genotype 1 infection. *J Hepatol* 2013; **58**: 467-472 [DOI: 10.1016/j.jhep.2012.11.017]

59 **Abu-Mouch S**, Fireman Z, Jarchovsky J, Zeina AR, Assy N. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naïve patients. *World J Gastroenterol* 2011; **17**: 5184-5190 [PMID: 22215943 DOI: 10.3748/wjg.v17.i47.5184]

60 **Nimer A**, Mouch A. Vitamin D improves viral response in hepatitis C genotype 2-3 naïve patients. *World J Gastroenterol* 2012; **18**: 800-805 [PMID: 22371640 DOI: 10.3748/wjg.v18.i8.800]

61 **Chang ML**, Hu JH, Yen CH, Chen KH, Kuo CJ, Lin MS, Lee CH, Chen SC, Chien RN. Evolution of ferritin levels in hepatitis C patients treated with antivirals. *Sci Rep* 2020; **10**: 19744 [PMID: 33184464 DOI: 10.1038/s41598-020-76871-z]

62 **Zou DM**, Sun WL. Relationship between Hepatitis C Virus Infection and Iron Overload. *Chin Med J (Engl)* 2017; **130**: 866-871 [PMID: 28345552 DOI: 10.4103/0366-6999.202737]

63 **Fujita N**, Sugimoto R, Takeo M, Urawa N, Mifuji R, Tanaka H, Kobayashi Y, Iwasa M, Watanabe S, Adachi Y, Kaito M. Hepcidin expression in the liver: relatively low level in patients with chronic hepatitis C. *Mol Med* 2007; **13**: 97-104 [PMID: 17515961 DOI: 10.2119/2006-00057.Fujita]

64 **Petta S**, Ciminnisi S, Di Marco V, Cabibi D, Cammà C, Licata A, Marchesini G, Craxì A. Sarcopenia is associated with severe liver fibrosis in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2017; **45**: 510-518 [PMID: 28028821 DOI: 10.1111/apt.13889]

65 **Gowda C**, Compher C, Amorosa VK, Lo Re V 3rd. Association between chronic hepatitis C virus infection and low muscle mass in US adults. *J Viral Hepat* 2014; **21**: 938-943 [PMID: 24989435 DOI: 10.1111/jvh.12273]

66 **Dasarathy S**. Cause and management of muscle wasting in chronic liver disease. *Curr Opin Gastroenterol* 2016; **32**: 159-165 [PMID: 26974417 DOI: 10.1097/MOG.0000000000000261]

67 **Gumucio JP**, Qasawa AH, Ferrara PJ, Malik AN, Funai K, McDonagh B, Mendias CL. Reduced mitochondrial lipid oxidation leads to fat accumulation in myosteatosis. *FASEB J* 2019; **33**: 7863-7881 [PMID: 30939247 DOI: 10.1096/fj.201802457RR]

68 **Fernández-Mincone T**, Contreras-Briceño F, Espinosa-Ramírez M, García-Valdés P, López-Fuenzalida A, Riquelme A, Arab JP, Cabrera D, Arrese M, Barrera F. Nonalcoholic fatty liver disease and sarcopenia: pathophysiological connections and therapeutic implications. *Expert Rev Gastroenterol Hepatol* 2020; **14**: 1141-1157 [PMID: 32811209 DOI: 10.1080/17474124.2020.1810563]

69 **Cruz-Jentoft AJ**, Sayer AA. Sarcopenia. *Lancet* 2019; **393**: 2636-2646 [PMID: 31171417 DOI: 10.1016/S0140-6736(19)31138-9]

70 **Zhai Y**, Xiao Q. The Common Mechanisms of Sarcopenia and NAFLD. *Biomed Res Int* 2017; **2017**: 6297651 [PMID: 29387723 DOI: 10.1155/2017/6297651]

71 **Hsu CS**, Kao JH. Sarcopenia and chronic liver diseases. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 1229-1244 [PMID: 30791794 DOI: 10.1080/17474124.2018.1534586]

72 **Hiraoka A**, Michitaka K, Ueki H, Kaneto M, Aibiki T, Okudaira T, Kawakami T, Yamago H, Suga Y, Tomida H, Miyamoto Y, Azemoto N, Mori K, Miyata H, Tsubouchi E, Ninomiya T, Hirooka M, Abe M, Matsuura B, Hiasa Y. Sarcopenia and two types of presarcopenia in Japanese patients with chronic liver disease. *Eur J Gastroenterol Hepatol* 2016; **28**: 940-947 [PMID: 27232361 DOI: 10.1097/MEG.0000000000000661]

73 **Kalafateli M**, Konstantakis C, Thomopoulos K, Triantos C. Impact of muscle wasting on survival in patients with liver cirrhosis. *World J Gastroenterol* 2015; **21**: 7357-7361 [PMID: 26139982 DOI: 10.3748/wjg.v21.i24.7357]

74 **Poynard T**, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; **349**: 825-832 [PMID: 9121257 DOI: 10.1016/s0140-6736(96)07642-8]

75 **Deuffic-Burban S**, Poynard T, Valleron AJ. Quantification of fibrosis progression in patients with chronic hepatitis C using a Markov model. *J Viral Hepat* 2002; **9**: 114-122 [DOI: 10.1046/j.1365-2893.2002.00340.x]

76 **Di Martino V**, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, Moussalli J, Thabut D, Buffet C, Poynard T. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. *Hepatology* 2004; **40**: 1426-1433 [PMID: 15565616 DOI: 10.1002/hep.20463]

77 **El Kassas M**, Salah E, Gad A, Hosny A. Improvement of sexual dysfunction in patients after treatment of hepatitis C virus using directly acting antivirals. *Curr Med Res Opin* 2021; **37**: 967-972 [PMID: 33688780 DOI: 10.1080/03007995.2021.1901677]

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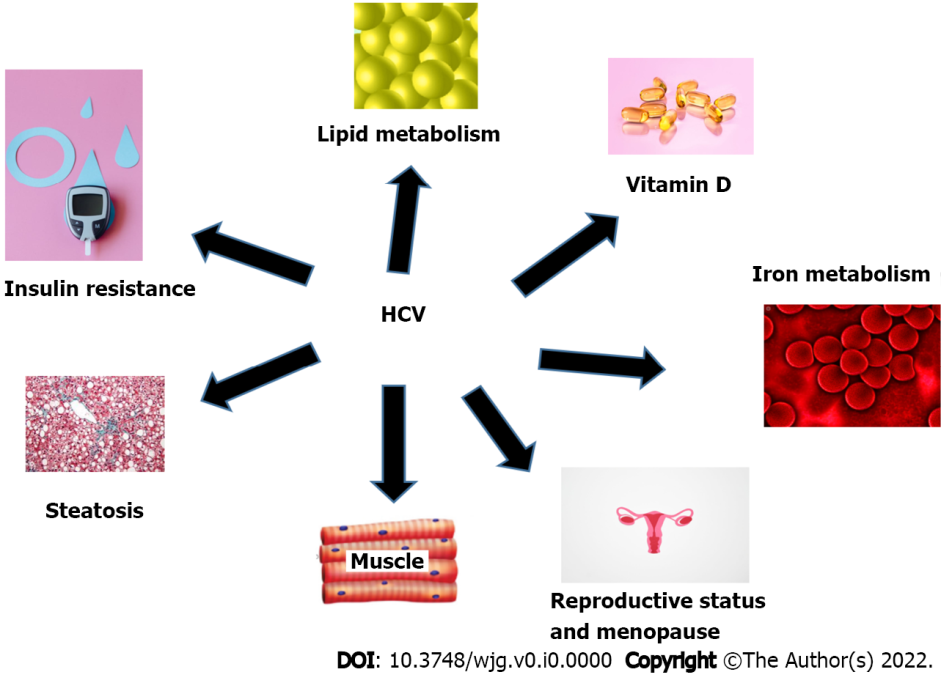
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**Figure Legends**



**Figure 1 Metabolic aspects of hepatitis C virus.** HCV: Hepatitis C virus.