REVIEW
2403 Prehabilitation prior to intestinal resection in Crohn’s disease patients: An opinion review
Bak MTJ, Ruiterkamp MFE, van Ruler O, Campmans-Kuijpers MJE, Bongers BC, van Meeteren NLU, van der Woude CJ, Stassen LPS, de Vries AC

2417 Hepatocellular carcinoma, hepatitis C virus infection and miRNA involvement: Perspectives for new therapeutic approaches

MINIREVIEWS
2429 Metabolic aspects of hepatitis C virus
El-Kassas M, Awad A

ORIGINAL ARTICLE
Basic Study
2437 18β-glycyrrhetinic acid regulates mitochondrial ribosomal protein L35-associated apoptosis signaling pathways to inhibit proliferation of gastric carcinoma cells

Retrospective Study
2457 Application of endoscopic ultrasonography for detecting esophageal lesions based on convolutional neural network
Liu GS, Huang PY, Wen ML, Zhuang SS, Hua J, He XP

2468 Prognostic value of preoperative enhanced computed tomography as a quantitative imaging biomarker in pancreatic cancer
Gao JF, Pan Y, Lin XC, Lu FC, Qiu DS, Liu JJ, Huang HG

2482 Endoscopic classification and pathological features of primary intestinal lymphangiectasia

Observational Study
2494 Accurate and generalizable quantitative scoring of liver steatosis from ultrasound images via scalable deep learning
Li B, Tai DI, Yan K, Chen YC, Chen CJ, Huang SF, Hsu TH, Yu WT, Xiao J, Le L, Harrison AP

Randomized Controlled Trial
2509 Saccharomyces cerevisiae I-3856 in irritable bowel syndrome with predominant constipation
LETTER TO THE EDITOR

2523 Future therapies for pancreatic carcinoma: Insights into cancer precision medicine

Jiang QY, Chen ZX, Zhang S, Xue RY
ABOUT COVER

Editorial Board of World Journal of Gastroenterology, Conrado M Fernandez-Rodriguez, MD, PhD, Associate Professor, Unit of Gastroenterology, Hospital Universitario Fundacion Alcorcon, Av. Budapest-1, Alcorcón, Madrid 28922, Spain. cfernandez@fhalcorcon.es

AIMS AND SCOPE

The primary aim of World Journal of Gastroenterology (WJG, World J Gastroenterol) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG’s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Hua-Ge Yu; Production Department Director: Xu Guo; Editorial Office Director: Ze-Mao Gong.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
June 14, 2022

COPYRIGHT
© 2022 Baishideng Publishing Group Inc
Metabolic aspects of hepatitis C virus

Mohamed El-Kassas, Abeer Awad

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

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.
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-a 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 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].

### VISERIAL 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[52], 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[53]. 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\cite{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\cite{66,67}. The association between CHC infection of the liver and muscle loss is well documented\cite{68,69}. High body mass index, IR, diabetes, hepatic steatosis, increased inflammation, increased oxidative stress, lipotoxicity, and multiple factors involved in muscle depletion are all considered as independent risk factors that predispose patients with CHC to skeletal muscle disorders\cite{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\cite{74,75}. Another report stated that long-term hormonal replacement therapy could prevent accelerated liver fibrosis in menopausal women with CHC\cite{76}. Noteworthy improvement in sexual dysfunction was reported in males and females after HCV treatment with direct-acting antivirals\cite{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.

FOOTNOTES

Author contributions: El-Kassas M conceptualized the idea, revised and edited the final manuscript; Awad A drafted the manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Egypt

ORCID number: Mohamed El-Kassas 0000-0002-3396-6894; Abeer Awad 0000-0001-9945-9767.

Corresponding Author’s Membership in Professional Societies: Egyptian Association for Research and Training in Hepatogastroenterology, No. 01.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

C patients. Vitamin D serum levels and its common genetic determinants, with severity of liver fibrosis in genotype 1 chronic hepatitis C patients.

Petta S, Miyajima I, Lee MH, Butt AA, European chronic HCV genotype 1 patients during and after treatment with pegylated interferon-α-2a and ribavirin. 


Cástrera L, Hézode C, Roudot-Thoraval F, Bastie A, Zafrañi ES, Pawlotsky JM, Dheumaux 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]

Mihm S. Hepatitis C virus, diabetes and steatosis: clinical evidence in favor of a linkage and role of genotypes. 

Diabetes Metab 2010; 28: 280-284 [PMID: 20460924 DOI: 10.1159/000282103]


Persico M, Lolascon A. Steatosis as a co-factor in chronic liver diseases. 


Younossi ZM, Stepanska M, Nader F, Younossi Z, Elsheikh E. Associations of chronic hepatitis C with metabolic and cardiovascular outcomes. 


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. 


Gastroenterology 2006; 130: 1636-1642 [PMID: 16697727 DOI: 10.1053/j.gastro.2006.03.014]


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 viral antiviral long-term treatment against cirrhosis trial. 

Gastroenterology 2009; 137: 549-557 [PMID: 19445938 DOI: 10.1053/j.gastro.2009.05.007]

Yoshimura T, Oppenheim JJ. Chemerin reveals its chimeric nature. 


Kanda T, Moriyama M. Direct-acting antiviral agents against hepatitis C virus and lipid metabolism. 


Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. 


Gut 2007; 56: 1105-1110 [PMID: 16956918 DOI: 10.1136/gut.2006.091983]

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]


J Gastroenterol 2013; 48: 93-100 [PMID: 22627845 DOI: 10.1007/s00535-012-0610-3]

Petta S, Grimaudo S, Marco VD, Scacozzone C, Macaluso FS, Cammà C, Cubidi B, Pipitone R, Craxi A. Association of vitamin D serum levels and its common genetic determinants, with severity of liver fibrosis in genotype 1 chronic hepatitis C patients. 
