
Hepatitis C–Associated Diabetes Mellitus

Ines Bilić-Ćurčić, Hrvoje Roguljić, Marul Ivandić,
Aleksandar Včev, Robert Smolić and Martina Smolić

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.70721>

Abstract

Diabetes type 2 mellitus (T2DM) is the most common extrahepatic association of hepatitis C virus (HCV) infection. Substantial research has suggested that insulin resistance (IR) has crucial importance in development of type 2 diabetes in HCV-infected patients. Several pathophysiological mechanisms are proposed, such as direct effect of HCV proteins on inhibition of the insulin-signaling pathway inducing central insulin resistance (IR), while overproduction of inflammatory cytokines and increased lipolysis promote peripheral IR. IR in HCV-infected patients is associated with impaired sustained virologic response (SVR) and higher incidence of hepatocellular carcinoma (HCC). Some, but not all, studies have shown improvements in achieving SVR in patients with interferon/ribavirin (RBV) therapy co-treated with metformin or pioglitazone as well as beneficiary effect on the incidence of hepatocellular carcinoma. Recent studies indicate that response to the new direct-acting antiviral (DAA) treatments is unaffected by insulin resistance thus diminishing importance of IR in the new era of DAA. Additionally, viral eradication by DAAs has been shown to ameliorate insulin resistance, attenuating the risk of new-onset diabetes type 2. However, those metabolic improvements are sustainable long after the treatment remains unclear.

Keywords: hepatitis C infection, diabetes type 2, insulin resistance, insulin signaling, antiviral agents

1. Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia, which in vast majority of cases fall into two broad etiopathogenetic categories: type 1 (T1DM) and type 2 diabetes mellitus (T2DM) [1, 2]. Frequency of type 1 is relatively low in comparison with type 2, which accounts for over 90% of cases globally [3]. For development of type 2 diabetes mellitus, several pathophysiological mechanisms are responsible such as insulin resistance

(IR), impairment of insulin secretion, and increased hepatic glucose production [4]. Chronic and uncontrolled diabetes results in serious comorbidities such as retinopathy, neuropathy, nephropathy, and cardiovascular diseases a leading cause of mortality [5].

So far, numerous studies indicate that diabetes mellitus could be the most common extrahepatic manifestation of chronic hepatitis C virus (HCV) [6]. A meta-analysis of 34 studies confirmed a positive correlation between HCV infection and increased prevalence of diabetes mellitus type 2 in comparison with general population [7]. Additionally, many epidemiological studies indicate that HCV-infected patients have higher prevalence of diabetes in comparison with hepatitis B virus (HBV)-infected patients [8].

2. Diabetes type 2 and chronic hepatitis C infection

Although HCV infection is primarily affecting liver, there are other well-known extrahepatic manifestations of chronic hepatitis C [9, 10]. Mechanisms of those disorders are related to extrahepatic tropism of the HCV or by immunological process in which chronic infection leads to the development of autoimmune-mediated disease [11].

Since the discovery of HCV in 1989, great attention is paid to the development of type 2 diabetes mellitus during chronic hepatitis C virus infection [12]. Already in 1994, Allison et al. showed that 50% of HCV-related cirrhosis have diabetes mellitus compared to 9% with cirrhosis related to other causes [13]. For a long time, a loss of liver endocrine function due to progression of fibrosis in chronic hepatitis was considered to be responsible for the development of insulin resistance [14]. To examine the effect of HCV infection without concomitant cirrhosis on development of diabetes mellitus, Knobler et al. performed an oral glucose tolerance test in patients with chronic hepatitis B and C without cirrhosis [15]. Study showed that 33% of HCV patients had type 2 diabetes, whereas only 12% of patients with chronic hepatitis B (HBV) infection and 6% of healthy volunteers had glucose metabolism impairment, indicating that diabetes occurs in the early stages of the HCV-induced liver disease. Also, liver biopsies from HCV-infected patients with diabetes had significantly higher fibrosis grade, inflammatory activity, and steatosis compared to HCV patients without diabetes.

The correlation between genotype of HCV and the level of insulin resistance has also been recognized. In a study of Hui, significantly lower insulin resistance index (HOMA-IR) was registered in patients with genotype 3 HCV in comparison with other genotypes [16]. Another study showed significantly higher median HOMA-IR in patients with hepatic steatosis infected with genotype 1 HCV than in patients with genotype 3 [17]. On the other hand, patients with genotype 3 had a higher probability of having moderate-to-severe steatosis, compared to those with non-3 genotypes [18]. Moreover, in type 1 genotype fatty liver disease occurred if there are other risk factors present at time like diabetes, adiposity, and insulin resistance implicating specific viral sequences responsible for fat accumulation independently of other risk factors. To clarify, there are two distinct disorders, viral, and metabolic steatosis [19]. This is important since whatever the mechanism, viral steatosis does not seem to impact liver fibrosis progression rate, although HCV genotype 3 is independently associated with

increased fibrosis progression. Also, viral steatosis does not impair response to interferon- α (IFN- α). Alternatively, steatosis due to the metabolic syndrome and IR is associated with both accelerated fibrosis progression and poor response to IFN- α -based therapy.

2.1. Hepatitis C–induced insulin resistance

Substantial research has suggested that insulin resistance has crucial importance in development of type 2 diabetes in HCV-infected patients [17]. A study of Hui et al. showed higher levels of insulin, C peptide, and HOMA-IR in 121 hepatitis C virus patients with stage 0 or 1 hepatic fibrosis compared with healthy controls proposing that HCV may induce IR irrespective to stage of liver fibrosis [16], although higher levels of liver fibrosis were associated with increased stage of insulin resistance. These findings were confirmed with other studies, and dependence of insulin resistance is determined with severity of liver fibrosis [6].

HCV-infected patients also develop insulin resistance in hepatic and peripheral tissues while pathogenetic mechanism is not clear [20]. Although HCV is hepatotropic virus, its genome has been detected in numerous extrahepatic tissues including pancreatic acinar cells and epithelial cells of pancreatic duct [21, 22]. Several studies demonstrated direct effect of the HCV proteins on inhibition of the insulin-signaling pathway. Key mediators of insulin-signaling cascade are insulin receptor substrate (IRS) 1 and 2. Disruption of IRS1 results in insulin resistance, while for development of diabetes mellitus, disruption of IRS2 is needed [23, 24]. In HCV, core-transgenic mice as well core-transfected human hepatoma cells downregulation of IRS1 and IRS2 were observed [25]. A proposed mechanism was that HCV core protein induced upregulation of suppressor of cytokine signaling (SOCS) 3 resulting in proteasomal degradation of IRS1 and IRS2 through ubiquitination. Furthermore, Alberstein et al. reported several impairments in the insulin-signaling cascade linked to a proteasome degradation of IRS1 protein in cell lines transfected with HCV core protein [26]. HCV infection increased gluconeogenesis by promoting the expression of gluconeogenic genes, such as glucose 6 phosphatase (G6P) and phosphoenolpyruvate carboxyl kinase 2 (PCK2), which had adverse effect on insulin resistance [19]. On the other hand, HCV downregulated the expression of glucose transporter GLUT 4, which resulted in decreased glucose uptake and increased level of glucose in plasma leading to impairment of glucose metabolism [27].

Also, HCV core protein of genotype 3 downregulated peroxisome proliferator activating receptor (PPAR γ) and upregulated SOCS 7 [28]. Beside its effect on insulin-signaling cascade, it is suggested that HCV has the ability to cause dysfunctions of cell organelles such as mitochondria and endoplasmatic reticulum which leads to further impairment of insulin-signaling pathway [29].

In studies where euglycemic insulin clamp was used, insulin resistance was determined mainly in peripheral tissues such as skeletal muscle rather than in liver [30]. Clearly, the effect of cytokines was necessary for the development of peripheral insulin resistance due to the tropism of HCV for hepatic tissue. Several studies emphasized the role of the overproduced tumor necrosis factor alpha (TNF- α) in HCV-induced insulin resistance [31–33]. Inhibitory role of TNF- α is achieved through activation of serine/threonine kinases, which resulted in uncoupling of insulin receptor substrate protein from downstream effectors [34]. Furthermore,

the importance of the TNF- α in HCV-induced IR was confirmed by the study of Shintani et al., which used transgenic mice with characteristic expression of HCV core protein in the liver. Insulin resistance and impaired glucose metabolism were observed in this transgenic model, while administration of an antitumor necrosis factor-alpha antibody restored insulin sensitivity [35]. TNF α -induced insulin resistance was also achieved through indirect mechanisms such as increased lipolysis resulting in regulation of expression of several adipocyte genes that modulate insulin sensitivity [36]. Dysfunction of lipid metabolism triggers lipotoxicity through increased production of free fatty acids, which promotes insulin resistance [37]. Along TNF- α , it is proposed that some other cytokines such as IL-6 and numerous adipokines have a role in pathogenesis of HCV-induced IR as well in steatosis of nonalcoholic fatty liver disease [38, 39]. Possible pathophysiological mechanisms of HCV-induced IR are shown in **Figure 1**.

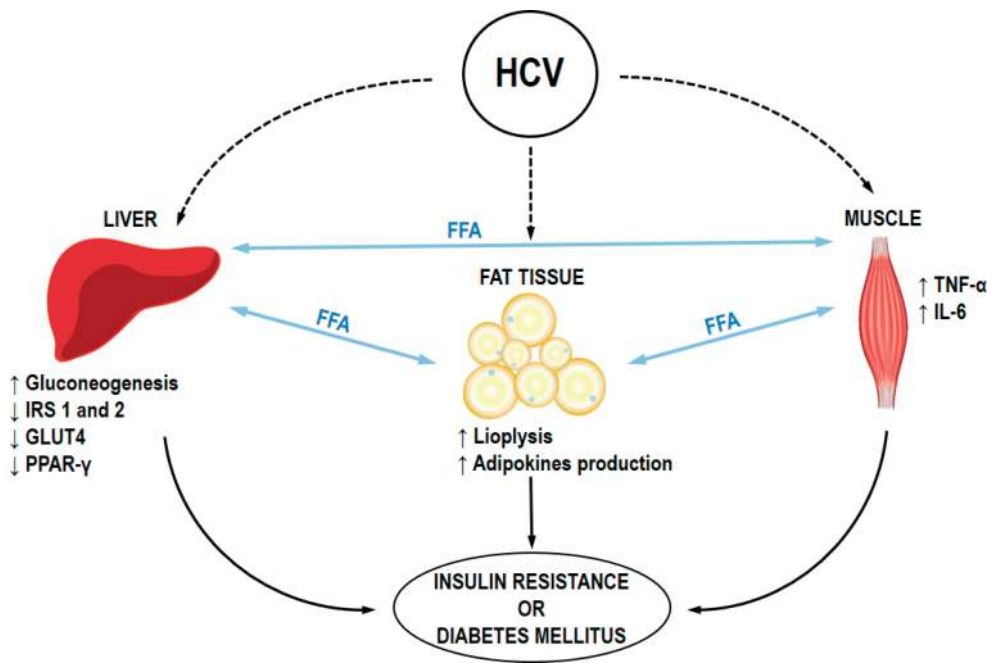


Figure 1. Proposed mechanisms involved in pathogenesis of HCV-induced insulin resistance and diabetes type 2.

3. Treatment of insulin resistance and diabetes with the eradication of viral infection

If HCV is one of the causal factors of insulin resistance, then clearance of viremia might be a way to reduce IR [40]. Additionally, viral eradication has been shown to ameliorate insulin resistance, attenuating the risk of new-onset T2DM [41].

Several observational studies indicated that eradication of HCV with interferon (IFN) and ribavirin (RBV) is associated with improved insulin sensitivity [42–44]. There are case reports that describe improvements in glycemic control with both IFN/RBV and IFN/RBV/telaprevir treatment. However, those improvements were observed only during the treatment phase, with the recurrence of diabetes when antiviral therapy ended [45, 46]. Case report by Doyle et al. was first to demonstrate complete remission of diabetes with viral clearance beyond the treatment phase, which may be due to the differences in antiviral treatment response [47]. In addition, several studies reported decreasing number of patients with IR treated with interferon IFN/RBV therapies after achievement of sustained virologic response (SVR) [40, 48–50]. Viral clearance is the most possible mechanism through which antiviral therapy ameliorates IR rather than a direct pharmacological effect of IFN/RBV.

A few studies [42, 43, 50] reported reduced incidence of T2DM among patients who achieved SVR. Although T2DM occurrence is associated with a genetic predisposition, it is also influenced by lifestyle-related aspects. For instance, one study showed that viral eradication induced a two-third reduction in the risk of T2DM incidence, but the authors did not report data regarding family history, smoking habit, and physical activity [42]. Reduced incidence of IR and T2DM in chronic hepatitis C (CHC) patients who achieved SVR after therapy, most likely depended on the genetic, demographic, clinical, histological, and lifestyle characteristics of the patients. For this reason, counseling on diet and physical activity should not be excluded by the eradication of HCV in patients with predisposing factors for T2DM.

The clinical impact of successful antiviral therapy on the long-term outcome of T2DM in diabetics with CHC is still unknown, mainly because of the lack in proper prospective studies although data from population-based research in Taiwan reported improved renal and cardiovascular outcomes in diabetic patients treated with antiviral HCV treatment [41].

High therapeutic efficacy of direct-acting antivirals (DAAs) will ensure viral eradication in a large number of diabetic cirrhotic patients, which will enable better understanding of the impact of the virus on T2DM outcome. One retrospective study reported a significant decrease in glycated hemoglobin (HbA1C) 6 months after HCV eradication with sofosbuvir, although the mechanism responsible for this improvement remains unknown [51]. In addition, other studies demonstrated the efficacy of DAAs (telaprevir and danoprevir) in improving IR and even restoring insulin sensitivity after achieving SVR, but only in genotype 1 patients [52, 53]. However, data for DAA effect on insulin resistance in other genotype HCV infected patients are lacking thus future studies are needed to conclude whether this effect is achievable in all genotypes.

4. Influence of insulin resistance and diabetes mellitus in treatment of hepatitis C infection

Since patients with chronic hepatitis C infection are twofold to threefold more likely to develop type 2 diabetes, which reduces their chances of achieving a sustained virologic response, the question is can we achieve better SVR by reducing insulin resistance. A meta-analysis of 17

studies has shown that insulin sensitivity was associated with a higher rate of SVR in comparison with insulin resistance. Elevated HOMA-IR was associated with a lower cure rate of patients with hepatitis C treated with Peg-IFN- α /ribavirin irrespective of genotype, and the more difficult-to-treat cohort, the better the HOMA-IR prediction [54]. In addition, IR was associated with a higher incidence of hepatocellular carcinoma (HCC) in patients with hepatitis C virus [55], thus improving IR and correcting hyperinsulinemia may improve the prognosis of HCV cirrhosis.

Therapy for the T2DM in patients with liver diseases is generally the same as that without liver disease. Only patients with evidence of liver cirrhosis have altered drug metabolism, and there is no evidence that patients with liver disease are predisposed to hepatotoxicity [56].

4.1. Biguanides

Metformin is considered as the drug of choice in HCV patients with IR or T2DM since it generally does not cause hepatotoxicity [57], although there are sporadic case reports of metformin induced acute liver injury [58]. Some, but not all studies, have shown improvements in achieving SVR in patients with interferon/ribavirin therapy co-treated with metformin

	Study population/design	Treatment	Outcome	Results
Yu et al. [59]	98 genotype 1 CHC patients with IR/Prospective study	Metformin 500 TID vs. placebo	SVR	59.2 vs. 38.8% (p = 0.43)
Romero-Gomez et al. [60]	123 genotype 1 CHC with IR/Prospective study	Metformin 850 mg TID vs. placebo	SVR	53 vs. 42%, p = NS
Sharifi et al. [61]	140 CHC patients/Prospective study	Metformin 500 mg TID vs. Placebo	SVR	75 vs. 79%, p = NS
Nkontchou et al. [62]	100 diabetic patients with HCV cirrhosis/Prospective study	Metformin, dose varied vs. therapy without metformin	Incidence of HCC	9.5 vs. 31.2% (p = .001)
Lee et al. [63]	800,000 health insurance beneficiaries/Prospective study	Metformin vs. no metformin in diabetic patients	HCC, colorectal, pancreatic cancer incidence	Reduced incidence to almost non-diabetic levels (HR, 0.12), p = significant
Chen et al. [64]	53 diabetic and 82 nondiabetic patients with HCC undergoing RFA/Retrospective study	Metformin in diabetic patients (varied dose) vs. therapy without metformin	Survival probability	1 year, 95 vs. 74.5% 5 years, 60.5 vs. 26.2%
Donadon et al. [65]	465 HCC, 618 liver cirrhosis, 490 control patients/Retrospective study	Metformin in diabetic control and LC patients vs. SU and insulin	Risk of HCC	>80% risk reduction, p = significant

Table 1. Summary of trials evaluating metformin use in patients with chronic HCV and T2DM or IR.

[59–61] (**Table 1**). Increasing evidence points out that metformin is independently associated with reduced risk for HCC and liver-related death/transplantation [62–65] (**Table 1**). Metformin is frequently discontinued once cirrhosis is diagnosed because of concerns about an increased risk of adverse effects in patients with liver impairment. However, the study from Zhang et al. on 250 diabetic patients who developed cirrhosis showed that patients who continued metformin had a significantly longer median survival than those who discontinued metformin. In other words, metformin was found to be an independent predictor of better survival [66]. It is reasonable to conclude that metformin should remain a first-line option for patients with T2DM and chronic compensated HCV; however, more prospective, randomized controlled trials are needed to confirm safety and efficacy of metformin.

4.2. Thiazolidinediones

Thiazolidinediones (TZDs) are the only real insulin sensitizers available as they act primarily through stimulation peroxisome proliferator-activated receptor PPAR- γ decreasing insulin resistance in the liver and peripheral tissues. However, only few studies showed that pioglitazone improved virologic response to peginterferon alpha-2b/ribavirin combination therapy in overweight hepatitis C genotype 4 patients, while there was no effect in other genotypes [67–70] (**Table 2**). Also, recent data suggested that pioglitazone could decrease a risk of HCC recurrence in the group of patients with a BMI ≥ 24 [71] (**Table 2**).

	Study population/design	Treatment	Outcome	Results
Khatab et al. [68]	Ninety-seven previously untreated patients with CHC and IR/Prospective study	Pioglitazone vs. no pioglitazone + standard care PegIFN/RBV	SVR	SVR was significantly higher with pioglitazone ($p = 0.04$)
Harrison et al. [69]	150 treatment-naive HCV genotype 1 patients/Prospective study	Pioglitazone vs. no pioglitazone + standard care PegIFN/RBV	SVR	No significant difference between groups
Marks et al. [70]	19 previous non responders to PegIFN-RBV/Pilot study	Pioglitazone vs. no pioglitazone during 24 week before PegIFN/RBV/PIO	SVR	15% achieved SVR, no significant difference
Sumie et al. [71]	85 HCV-infected HCC patients/Prospective study	Pioglitazone vs. no pioglitazone in therapy	Recurrence-free survival	No significant difference, except in a group with BMI >24 kg/m ²

Table 2. Summary of trials evaluating pioglitazone use in patients with chronic HCV and T2DM or IR.

TZD use is not recommended in advanced liver cirrhosis because of the reported cases of acute cholestatic hepatitis [72]. Current recommendation is that serum ALT levels are evaluated before the initiation of rosiglitazone and pioglitazone therapy and that therapy should not be initiated if there is evidence of active liver disease.

4.3. Incretin mimetics

Incretins are gut-derived hormones, mainly glucagon-like peptide 1 (GLP-1) and glucose-dependent insulintropic peptide (GIP), that are secreted at low basal levels in the fasting state. Circulating levels increase rapidly and transiently following food ingestion. GLP-1R agonists control blood glucose through regulation of islet function, principally through activation of insulin-secreting beta cell in pancreas, and inhibition of glucagon secretion. In short term, it enhances glucose-induced insulin secretion, but continuous GLP-1 receptor activation also increases insulin synthesis, and beta cell proliferation and neogenesis. Dipeptidyl peptidase (DPP)-4 inactivates incretin hormones including GLP-1. Therefore, GLP-1 agonists as well as (DPP)-4 inhibitors are used as antidiabetic agents [73, 74].

Itou et al. found decreased serum GLP-1 levels and increased DPP-4 expression in the ileum, liver, and serum in HCV patients compared to control group and HBV group, thus concluding that altered expression of GLP-1 may play a role in the development of HCV-associated glucose intolerance [75]. Recent studies on GLP-1 have shown slowing of the progression of non-alcoholic fatty liver disease (NAFLD) by direct effects on lipid metabolism in hepatocytes, and on inflammation in the liver [76]. A case-control study reported a reduction in HbA1C without side effects when treating HCV patients with DPP-4 inhibitors [77]. Nevertheless, further larger studies are needed to support the use of incretin mimetics in patients with advanced hepatic diseases.

4.3.1. Insulin

Insulin has been considered as the drug of choice in patients with diabetes and decompensated liver disease due to short half-life. However, one study in Japan found that exogenous insulin and a second-generation sulfonylurea were associated with a higher incidence of HCC in hepatitis C patients [78], whereas other studies showed reduced risk of HCC with the use of metformin, compared with SUs and insulin [79]. One meta-analysis of observational studies summarized the impact of antidiabetic medication on the risk of HCC: insulin and sulfonylurea (SU) increased the risk, metformin reduced it, and TDZs did not change it [80]. Insulin requirements may vary because patients with decompensated liver disease can have decreased requirements due to reduced capacity for gluconeogenesis or an increased need for insulin due to insulin resistance. Thus, there is need for careful glucose monitoring and frequent dose adjustments of insulin.

In conclusion, traditionally medications used to overcome IR are metformin and thiazolidinediones, but their effect on SVR and incidence of HCC remains an open question. However, new promising agents such as GLP-1 receptor agonists could further improve outcome and prognosis of HCV-infected patients with metabolic disturbances.

5. Conclusion

Without a doubt, IR in HCV-infected patients is associated with impaired SVR and higher incidence of hepatocellular carcinoma as well as higher incidence of diabetes type 2 accompanied

by other metabolic disturbances. Evidence of beneficiary effect of metformin or pioglitazone co-treatment in patients with interferon/ribavirin therapy on achieving SVR or incidence of HCC in HCV patients are scarce and ambiguous, leaving more room for questions than offering potential solutions. However, recently published research suggests that response to the new direct-acting antiviral treatments is not dependent on insulin resistance thus diminishing importance of IR in the new era of DAA. Furthermore, if we postulate that HCV induces insulin resistance than achieving SVR could ameliorate it. Evidence supporting this hypothesis was recently published showing that insulin resistance disappeared after viral eradication by DAAs consequently decreasing a risk of diabetes type 2. In conclusion, further studies are needed to constitute how HCV induces insulin resistance, what effects different HCV therapies have on improving glycemic outcomes, and whether those metabolic improvements are permanent and still present after the treatment.

Author details

Ines Bilić-Ćurčić^{1,2*}, Hrvoje Roguljić^{1,2}, Marul Ivandić², Aleksandar Včev^{2,3}, Robert Smolić^{1,2} and Martina Smolić¹

*Address all correspondence to: ibcurcic@mefos.hr

1 Department of Pharmacology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

2 Clinic for Internal Medicine, University Hospital Center Osijek, Osijek, Croatia

3 Department of Internal Medicine, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

References

- [1] Balakumar P, Maung-U K, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacological Research*. 2016;**113**(Pt A):600-609
- [2] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Medicine*. 1998;**15**(7):539-553
- [3] Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001;**414**(6865):782-787
- [4] Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;**58**(4):773-795
- [5] Girach A, Manner D, Porta M. Diabetic microvascular complications: Can patients at risk be identified? A review. *International Journal of Clinical Practice*. 2006;**60**(11):1471-1483

- [6] Knobler H, Malnick S. Hepatitis C and insulin action: An intimate relationship. *World Journal of Hepatology*. 2016;**8**(2):131-138
- [7] White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: A systematic review and meta-analysis. *Journal of Hepatology*. 2008;**49**(5):831-844
- [8] Bose SK, Ray R. Hepatitis C virus infection and insulin resistance. *World Journal of Diabetes*. 2014;**5**(1):52-58
- [9] Cheng Z, Zhou B, Shi X, Zhang Y, Zhang L, Chen L, et al. Extrahepatic manifestations of chronic hepatitis C virus infection: 297 Cases from a tertiary medical center in Beijing, China. *Chinese Medical Journal* . 2014;**127**(7):1206-1210
- [10] Tang L, Marcell L, Kottitil S. Systemic manifestations of hepatitis C infection. *Infectious Agents and Cancer*. 2016;**11**:29
- [11] Gill K, Ghazinian H, Manch R, Gish R. Hepatitis C virus as a systemic disease: Reaching beyond the liver. *Hepatology International*. 2016;**10**(3):415-423
- [12] Antonelli A, Ferrari SM, Giuggioli D, Di Domenicantonio A, Ruffilli I, Corrado A, et al. Hepatitis C virus infection and type 1 and type 2 diabetes mellitus. *World Journal of Diabetes*. 2014;**5**(5):586-600
- [13] Allison ME, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. *Journal of Hepatology*. 1994;**21**(6):1135-1139
- [14] Romero-Gómez M. Insulin resistance and hepatitis C. *World Journal of Gastroenterology*. 2006;**12**(44):7075-7080
- [15] Knobler H, Schihmanter R, Zifroni A, Fenakel G, Schattner A. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. *Mayo Clinic Proceedings*. 2000;**75**(4):355-359
- [16] Hui JM, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression [corrected]. *Gastroenterology*. 2003;**125**(6):1695-1704
- [17] Fartoux L, Poujol-Robert A, Guéchet J, Wendum D, Poupon R, Serfaty L. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut*. 2005;**54**(7):1003-1008
- [18] Rubbia-Brandt L, Fabris P, Paganin S, Leandro G, Male PJ, Giostra E, et al. Steatosis affects chronic hepatitis C progression in a genotype specific way. *Gut*. 2004;**53**(3):406-412
- [19] Negro F. Facts and fictions of HCV and comorbidities: Steatosis, diabetes mellitus, and cardiovascular diseases. *Journal of Hepatology*. 2014 November;**61**(1 Suppl):S69-S78
- [20] Kawaguchi Y, Mizuta T. Interaction between hepatitis C virus and metabolic factors. *World Journal of Gastroenterology*. 2014;**20**(11):2888-2901

- [21] Gowans EJ, Jones KL, Bharadwaj M, Jackson DC. Prospects for dendritic cell vaccination in persistent infection with hepatitis C virus. *Journal of Clinical Virology*. 2004;**30**(4):283-290
- [22] Masini M, Campani D, Boggi U, Menicagli M, Funel N, Pollera M, et al. Hepatitis C virus infection and human pancreatic beta-cell dysfunction. *Diabetes Care*. 2005;**28**(4):940-941
- [23] Tamemoto H, Kadowaki T, Tobe K, Yagi T, Sakura H, Hayakawa T, et al. Insulin resistance and growth retardation in mice lacking insulin receptor substrate-1. *Nature*. 1994;**372**(6502):182-186
- [24] Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren JM, Previs S, et al. Disruption of IRS-2 causes type 2 diabetes in mice. *Nature*. 1998;**391**(6670):900-904
- [25] Kawaguchi T, Yoshida T, Harada M, Hisamoto T, Nagao Y, Ide T, et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *American Journal of Pathology*. 2004;**165**(5):1499-1508
- [26] Alberstein M, Zornitzki T, Zick Y, Knobler H. Hepatitis C core protein impairs insulin downstream signalling and regulatory role of IGFBP-1 expression. *Journal of Viral Hepatitis*. 2012;**19**(1):65-71
- [27] Bose SK, Shrivastava S, Meyer K, Ray RB, Ray R. Hepatitis C virus activates the mTOR/S6K1 signaling pathway in inhibiting IRS-1 function for insulin resistance. *Journal of Virology*. 2012;**86**(11):6315-6322
- [28] Bugianesi E, Salamone F, Negro F. The interaction of metabolic factors with HCV infection: Does it matter? *Journal of Hepatology*. 2012;**56**(Suppl 1):S56-S65
- [29] Kralj D, Virović Jukić L, Stojavljević S, Duvnjak M, Smolić M, Čurčić IB. Hepatitis C virus, insulin resistance, and steatosis. *Journal of Clinical and Translational Hepatology*. 2016;**4**(1):66-75
- [30] Milner KL, van der Poorten D, Trenell M, Jenkins AB, Xu A, Smythe G, et al. Chronic hepatitis C is associated with peripheral rather than hepatic insulin resistance. *Gastroenterology*. 2010;**138**(3):932-941.e1-3
- [31] Nelson DR, Lim HL, Marousis CG, Fang JW, Davis GL, Shen L, et al. Activation of tumor necrosis factor-alpha system in chronic hepatitis C virus infection. *Digestive Diseases and Sciences*. 1997;**42**(12):2487-2494
- [32] Hotamisligil GS. The role of TNFalpha and TNF receptors in obesity and insulin resistance. *Journal of Internal Medicine*. 1999;**245**(6):621-625
- [33] Zylberberg H, Rimaniol AC, Pol S, Masson A, De Groote D, Berthelot P, et al. Soluble tumor necrosis factor receptors in chronic hepatitis C: A correlation with histological fibrosis and activity. *Journal of Hepatology*. 1999;**30**(2):185-191
- [34] Zick Y. Uncoupling insulin signalling by serine/threonine phosphorylation: A molecular basis for insulin resistance. *Biochemical Society Transactions*. 2004;**32**(Pt 5):812-816

- [35] Shintani Y, Fujie H, Miyoshi H, Tsutsumi T, Tsukamoto K, Kimura S, et al. Hepatitis C virus infection and diabetes: Direct involvement of the virus in the development of insulin resistance. *Gastroenterology*. 2004;**126**(3):840-848
- [36] Ruan H, Hacoheh N, Golub TR, Van Parijs L, Lodish HF. Tumor necrosis factor-alpha suppresses adipocyte-specific genes and activates expression of preadipocyte genes in 3T3-L1 adipocytes: Nuclear factor-kappaB activation by TNF-alpha is obligatory. *Diabetes*. 2002;**51**(5):1319-1336
- [37] Unger RH, Orci L. Lipotoxic diseases of nonadipose tissues in obesity. *International Journal of Obesity and Related Metabolic Disorders*. 2000;**24**(Suppl 4):S28-S32
- [38] Cua IH, Hui JM, Bandara P, Kench JG, Farrell GC, McCaughan GW, et al. Insulin resistance and liver injury in hepatitis C is not associated with virus-specific changes in adipocytokines. *Hepatology*. 2007;**46**(1):66-73
- [39] Stojavljević S, Gomerčić Palčić M, Virović Jukić L, Smirčić Duvnjak L, Duvnjak M. Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease. *World Journal of Gastroenterology*. 2014;**20**(48):18070-18091
- [40] Delgado-Borrego A, Jordan SH, Negre B, Healey D, Lin W, Kamegaya Y, et al. Reduction of insulin resistance with effective clearance of hepatitis C infection: Results from the HALT-C trial. *Clinical Gastroenterology and Hepatology*. 2010;**8**(5):458-462
- [41] Hsu YC, Lin JT, Ho HJ, Kao YH, Huang YT, Hsiao NW, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. *Hepatology*. 2014;**59**(4):1293-1302
- [42] Arase Y, Suzuki F, Suzuki Y, Akuta N, Kobayashi M, Kawamura Y, et al. Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. *Hepatology*. 2009;**49**(3):739-744
- [43] Simó R, Lecube A, Genescà J, Esteban JI, Hernández C. Sustained virological response correlates with reduction in the incidence of glucose abnormalities in patients with chronic hepatitis C virus infection. *Diabetes Care*. 2006;**29**(11):2462-2466
- [44] Thompson AJ, Patel K, Chuang WL, Lawitz EJ, Rodriguez-Torres M, Rustgi VK, et al. Viral clearance is associated with improved insulin resistance in genotype 1 chronic hepatitis C but not genotype 2/3. *Gut*. 2012;**61**(1):128-134
- [45] Tahrani A, Bowler L, Singh P, Coates P. Resolution of diabetes in type 2 diabetic patient treated with IFN-alpha and ribavirin for hepatitis C. *European Journal of Gastroenterology and Hepatology*. 2006;**18**(3):291-293
- [46] Tallón de Lara P, Himschoot T, Frossard JL, Negro F. Does telaprevir possess a direct antidiabetic effect? *Liver International*. 2014;**34**(6):967-969
- [47] Doyle MA, Cooper C. Successful hepatitis C antiviral therapy induces remission of type 2 diabetes: A case report. *The American Journal of Case Reports*. 2015;**16**:745-750

- [48] Kawaguchi T, Ide T, Taniguchi E, Hirano E, Itou M, Sumie S, et al. Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *American Journal of Gastroenterology*. 2007;**102**(3):570-576
- [49] Kawaguchi Y, Mizuta T, Oza N, Takahashi H, Ario K, Yoshimura T, et al. Eradication of hepatitis C virus by interferon improves whole-body insulin resistance and hyperinsulinaemia in patients with chronic hepatitis C. *Liver International*. 2009;**29**(6):871-877
- [50] Romero-Gómez M, Fernández-Rodríguez CM, Andrade RJ, Diago M, Alonso S, Planas R, et al. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. *Journal of Hepatology*. 2008;**48**(5):721-727
- [51] Morales AL, Junga Z, Singla MB, Sjogren M, Torres D. Hepatitis C eradication with sofosbuvir leads to significant metabolic changes. *World Journal of Hepatology*. 2016;**8**(35):1557-1563
- [52] Moucari R, Forestier N, Larrey D, Guyader D, Couzigou P, Benhamou Y, Voitot H, Vidaud M, Seiwert S, Bradford B, Zeuzem S, Marcellin P. Danoprevir, an HCV NS3/4A protease inhibitor, improves insulin sensitivity in patients with genotype 1 chronic hepatitis C. *Gut*. 2010;**59**(12):1694-1698
- [53] Serfaty L, Forns X, Goeser T, Ferenci P, Nevens F, Carosi G, Drenth JP, Lonjon-Domanec I, DeMasi R, Picchio G, Beumont M, Marcellin P. Insulin resistance and response to telaprevir plus peginterferon α and ribavirin in treatment-naïve patients infected with HCV genotype 1. *Gut*. 2012 October;**61**(10):1473-1480
- [54] Eslam M, Aparcero R, Kawaguchi T, Del Campo JA, Sata M, Khattab MA, Romero-Gomez M. Meta-analysis: Insulin resistance and sustained virological response in hepatitis C. *Alimentary Pharmacology and Therapeutics*. 2011 August;**34**(3):297-305
- [55] Khattab MA, Eslam M, Mousa YI, Ela-adawy N, Fathy S, Shatat M, Abd-Aalhalim H, Kamal A, Sharawe MA. Association between metabolic abnormalities and hepatitis C-related hepatocellular carcinoma. *Annals of Hepatology*. 2012 July-August;**11**(4):487-494
- [56] Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes Care*. 2007;**30**(3):734-743
- [57] Hammerstad SS, Grock SF, Lee HJ, Hasham A, Sundaram N, Tomer Y. Diabetes and hepatitis C: A two-way association. *Front Endocrinol (Lausanne)*. 2015;**6**:134
- [58] Miralles-Linares F, Puerta-Fernandez S, Bernal-Lopez MR, Tinahones FJ, Andrade RJ, Gomez-Huelgas R. Metformin-induced hepatotoxicity. *Diabetes Care*. 2012;**35**(3):e21
- [59] Yu JW, Sun LJ, Zhao YH, Kang P, Yan BZ. The effect of metformin on the efficacy of antiviral therapy in patients with genotype 1 chronic hepatitis C and insulin resistance. *International Journal of Infectious Diseases*. 2012;**16**(6):e436-e441
- [60] Romero-Gómez M, Diago M, Andrade RJ, Calleja JL, Salmerón J, Fernández-Rodríguez CM, et al. Treatment of insulin resistance with metformin in naïve genotype 1 chronic hepatitis C patients receiving peginterferon alfa-2a plus ribavirin. *Hepatology*. 2009;**50**(6):1702-1708

- [61] Sharifi AH, Mohammadi M, Fakharzadeh E, Zamini H, Zaer-Rezaee H, Jabbari H, et al. Efficacy of adding metformin to pegylated interferon and ribavirin in treatment naïve patients with chronic hepatitis C: A randomized double-blind controlled trial. *Middle East Journal of Digestive Diseases*. 2014;**6**(1):13-17
- [62] Nkontchou G, Cosson E, Aout M, Mahmoudi A, Bourcier V, Charif I, et al. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. *Journal of Clinical Endocrinology & Metabolism*. 2011;**96**(8):2601-2608
- [63] Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, Huang YC. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: A representative population prospective cohort study of 800,000 individuals. *BMC Cancer*. 2011;**11**:20
- [64] Chen TM, Lin CC, Huang PT, Wen CF. Metformin associated with lower mortality in diabetic patients with early stage hepatocellular carcinoma after radiofrequency ablation. *Journal of Gastroenterology and Hepatology*. 2011;**26**(5):858-865
- [65] Donadon V, Balbi M, Valent F, Avogaro A. Glycated hemoglobin and antidiabetic strategies as risk factors for hepatocellular carcinoma. *World Journal of Gastroenterology*. 2010;**16**(24):3025-3032
- [66] Zhang X, Harmsen WS, Mettler TA, Kim WR, Roberts RO, Therneau TM, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology*. 2014;**60**(6):2008-2016
- [67] Chojkier M, Elkhayat H, Sabry D, Donohue M, Buck M. Pioglitazone decreases hepatitis C viral load in overweight, treatment naïve, genotype 4 infected-patients: A pilot study. *PLoS One*. 2012;**7**(3):e31516
- [68] Khattab M, Emad M, Abdelaleem A, Eslam M, Atef R, Shaker Y, Hamdy L. Pioglitazone improves virological response to peginterferon alpha-2b/ribavirin combination therapy in hepatitis C genotype 4 patients with insulin resistance. *Liver International*. 2010 March;**30**(3):447-454
- [69] Harrison SA, Hamzeh FM, Han J, Pandya PK, Sheikh MY, Vierling JM. Chronic hepatitis C genotype 1 patients with insulin resistance treated with pioglitazone and peginterferon alpha-2a plus ribavirin. *Hepatology*. 2012;**56**(2):464-473
- [70] Marks KM, Kitch D, Chung RT, Hadigan C, Andersen J, Tien P, et al. Pilot study of pioglitazone before HCV retreatment in HIV/HCV genotype 1-infected subjects with insulin resistance and previous nonresponse to peginterferon and ribavirin therapy: A5239. *Journal of Acquired Immune Deficiency Syndromes*. 2014;**65**(3):345-349
- [71] Sumie S, Kawaguchi T, Kawaguchi A, Kuromatsu R, Nakano M, Satani M, et al. Effect of pioglitazone on outcome following curative treatment for hepatocellular carcinoma in patients with hepatitis C virus infection: A prospective study. *Molecular and Clinical Oncology*. 2015;**3**(1):115-120

- [72] Bonkovsky HL, Azar R, Bird S, Szabo G, Banner B. Severe cholestatic hepatitis caused by thiazolidinediones: Risks associated with substituting rosiglitazone for troglitazone. *Digestive Diseases and Sciences*. 2002;**47**(7):1632-1637
- [73] Valverde I, Villanueva-Peñacarrillo ML, Malaisse WJ. Pancreatic and extrapancreatic effects of GLP-1. *Diabetes & Metabolism*. 2002;**28**(6 Pt 2):3S85-3S89 discussion 3S108-12
- [74] Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: Evaluation of the risks and benefits. *Diabetes Care*. 2010;**33**(2):428-433
- [75] Itou M, Kawaguchi T, Taniguchi E, Sumie S, Oriishi T, Mitsuyama K, et al. Altered expression of glucagon-like peptide-1 and dipeptidyl peptidase IV in patients with HCV-related glucose intolerance. *Journal of Gastroenterology and Hepatology*. 2008;**23**(2):244-251
- [76] Liu J, Wang G, Jia Y, Xu Y. GLP-1 receptor agonists: Effects on the progression of non-alcoholic fatty liver disease. *Diabetes/Metabolism Research and Reviews*. 2015;**31**(4):329-335
- [77] Arase Y, Kawamura Y, Seko Y, Kobayashi M, Suzuki F, Suzuki Y, et al. Efficacy and safety in sitagliptin therapy for diabetes complicated by non-alcoholic fatty liver disease. *Hepatology Research*. 2013;**43**(11):1163-1168
- [78] Kawaguchi T, Taniguchi E, Morita Y, Shirachi M, Tateishi I, Nagata E, et al. Association of exogenous insulin or sulphonylurea treatment with an increased incidence of hepatoma in patients with hepatitis C virus infection. *Liver International*. 2010;**30**(3):479-486
- [79] Donadon V, Balbi M, Mas MD, Casarin P, Zanette G. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver International*. 2010;**30**(5):750-758
- [80] Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: A systematic review and meta-analysis. *American Journal of Gastroenterology*. 2013;**108**(6):881-891 quiz 92

