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Chapter 10

Hepatitis C–Associated Diabetes Mellitus

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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, antidiabetic 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 pathophysiologic mechanisms are responsible such as insulin resistance

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(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-a (IFN-a). Alternatively, steatosis due to the metabolic syndrome and IR is associated with both accelerated fibrosis progression and poor response to IFN-a-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 (PPARγ) 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]. TNFα-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**.

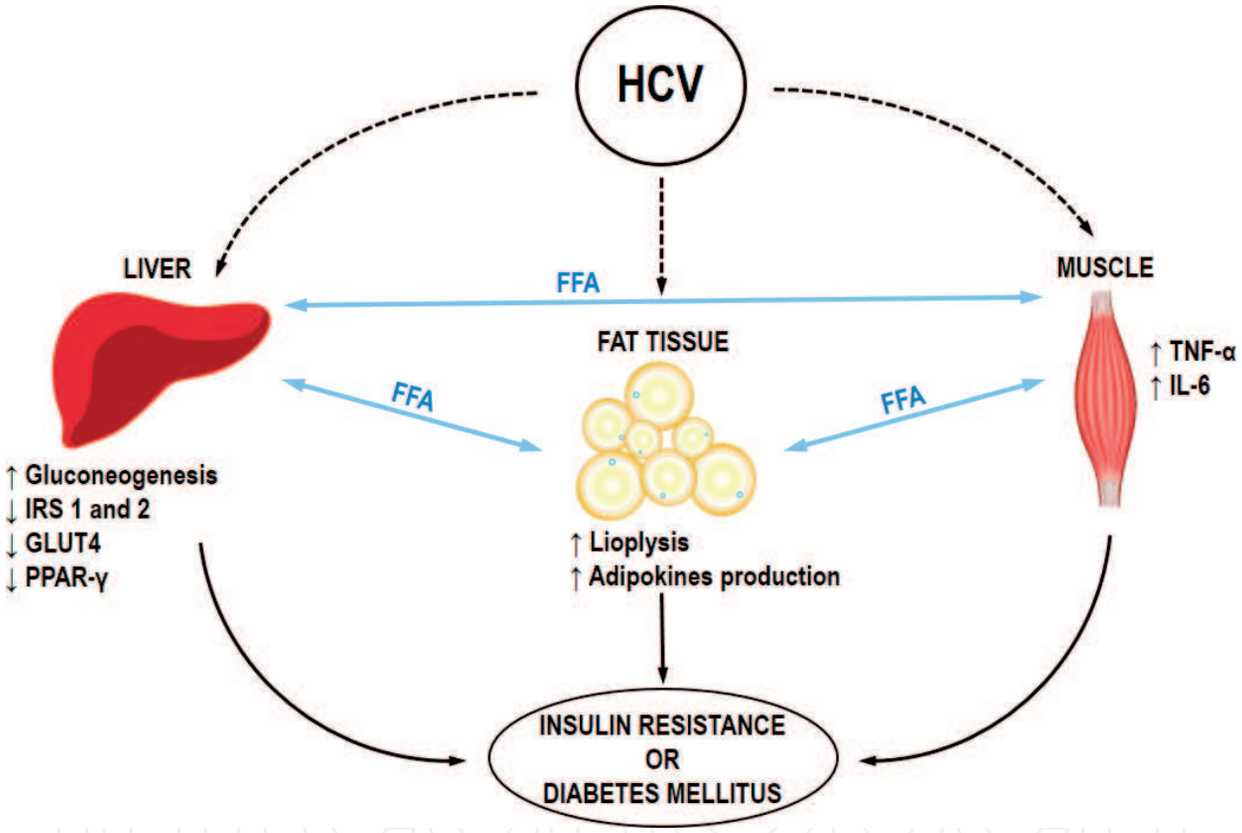

Figure 1. Proposed mechanisms involved in pathogenesis of HCV-induced insulin resistance and diabetes type 2.

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-Y 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
Khattab 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/m2

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 insulinotropic 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-acoholic 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.

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