Glucose abnormalities in hepatitis C virus infection

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Abstract
Hepatitis C virus (HCV) infection is one of the most important causes of cirrhosis and hepatocellular carcinoma and has a tremendous impact on public health worldwide. HCV is both hepatotropic and lymphotropic. Replication of HCV in diseased extrahepatic organs and tissues may either trigger latent autoimmunity or induce autoimmune disorders. In addition to established liver injury, type 2 diabetes mellitus (T2DM) is an important feature of extrahepatic metabolic disorders which is attributed to HCV infection. It also has some impact on the disease activity, disease course, clinical outcomes, and treatment efficacy of antiviral therapy. Previous experimental and clinical findings have highly suggested that HCV per se is diabetogenic. The cause–effect interaction between a common endocrine disorder and an infectious disease is an important issue to elucidate. Although the precise mechanisms whereby HCV infection leads to insulin resistance (IR) and glucose abnormalities are not entirely clear, it differs from the usual pathogenesis of T2DM in those with non-HCV liver diseases. This review initially highlights epidemiological and pathophysiological studies addressing the mutual link between chronic HCV infection (CHC) and T2DM. The characteristics of glucose abnormalities in this special population are depicted from the current evidence. The mutual roles of IR and CHC with respect to the prediction of treatment efficacy, how treatment response affects IR, and the role of pancreatic beta cell function in the entire suite are discussed. With the rapid progression of antiviral therapy for CHC in the past decade, we have also listed some points of future perspective in this issue.

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Introduction

Hepatitis C virus (HCV) infection and type 2 diabetes mellitus (T2DM) are two major rising epidemics which represent tough challenges both to clinicians and to healthcare systems in terms of diagnostic, therapeutic and economic implications. In 2003, over 194 million people were diagnosed with diabetes worldwide, with 333 million individuals predicted to be affected by 2025. These numbers, however, do not include those with undiagnosed diabetes, a population that is currently estimated to represent one-quarter of the US population alone. Furthermore, HCV infection currently affects 3% of the world population, estimated at 170 million people worldwide, which will lead to a substantial rise in the prevalence of chronic liver disease, with great health and economic impacts.

The liver has long been regarded as the key player manipulating the homeostasis of glucose metabolism. As the largest reservoir of glucose, the liver’s role in glucose metabolism draws much attention in patients with advanced liver disease. Insulin resistance (IR) is therefore a common feature of some liver diseases, especially at advanced stages. Hepatic diabetes was recognized when diabetes developed in patients who had advanced liver cirrhosis or severe liver injury, in which overt fasting hypoglycemia and/or postprandial hyperglycemia emerge as a common phenomenon. However, the association between T2DM and CHC is beyond the concept of hepatic diabetes. Although type 1 DM has been observed in patients who were treated with interferon (IFN), the majority of HCV-related diabetes is T2DM.

Epidemiological view

The association between T2DM and CHC was first reported in 1994 by Allison et al., who observed that the prevalence of T2DM was significantly higher in those with HCV-related cirrhosis than those with cirrhosis resulting from other liver diseases [1]. The diagnosis of HCV infection and the identification of risk factors for HCV infection preceded the diagnosis and/or onset of T2DM in anti-HCV(+) diabetic patients [2]. Generally, the prevalence of anti-HCV seropositivity in the T2DM population ranged from 1.8% to 12.1%, whereas T2DM developed in 14.5–33.0% of CHC patients [1,3–9]. Different background in terms of ethnicity, age, prevalence of T2DM, body mass index (BMI), viral load and genotype may contribute to the divergent results of the epidemiological observations. Huang et al., in a community-based case-controlled study composing serological and virological features of HCV infection, further extended the observation that HCV viremia, but not anti-HCV seropositivity alone, increased the association with T2DM (Fig. 1). HCV viremia was the most significant independent factor to be associated with T2DM in their multivariate logistic analysis, followed by well-established factors such as male gender, hypertension, BMI and age. It may imply that a persistent and/or active phase of HCV infection is associated with T2DM [10]. Wang et al. also observed that the 7-year cumulative incidence of those anti-HCV(+) patients was nearly doubled compared to those HBsAg+ and negative controls from a prospective community cohort aged 40 years or more without T2DM. After stratification by age and BMI, the risk ratio for T2DM in anti-HCV(+) participants increased as age decreased and BMI levels increased [11]. Taken together, a link between CHC and T2DM has been supported by robust epidemiological evidence [1,3,4,9,12]. T2DM represented one more disease to be included in the list of established extrahepatic manifestations of HCV infection.

The relationship between T2DM and HCV genotypes remains controversial [2,3,8,13]. Zignego et al. demonstrated that HCV genotype-2a (G-2a) was specifically linked with extrahepatic manifestations such as cryoglobulinemia [14]. An association between G-2a infection and T2DM was also shown [3]. Recently, a large-scale international collaborative study [15] addressing the association between IR and viral clearance in G-1, -2 and -3 patients showed that IR was more common in patients with G-1 than with G-2/3 infection. Viral eradication was associated with a reduction in IR in patients infected with G-1 but not in those with G-2/3 infection, suggesting a causal relationship between G-1 infection and IR in vivo. However, inconsistent observations have been shown in previous studies of different geographic regions [10,16].

Pathophysiologi cal view

T2DM is a common endocrine disorder encompassing multifactorial pathogenic mechanisms. These mechanisms include resistance to the action of insulin, increased hepatic glucose production, and a defect in insulin secretion, all of which contribute to the development of overt hyperglycemia [17]. As well as skeletal muscle and adipose tissue, liver is the major target for the metabolic actions of insulin. Insulin regulates glucose homeostasis by reducing hepatic glucose output and by increasing the rate of glucose uptake by skeletal muscle and adipose tissue. Therefore IR is a common feature of advanced liver diseases from various insults.

HCV has been shown to be a lymphotropic as well as a hepatotropic virus [18]. Replication of HCV in diseased
extrahepatic organs and tissues may have cytopathic effects [19]. The precise biological mechanisms whereby HCV infection leads to IR are not entirely clear. However, it does not follow the fashions of advanced liver disease as mentioned above. HCV may induce a Th1 lymphocyte immune-mediated response which leads to activation of the tumor necrosis factor (TNF)-α system and elevation of interleukin-6 levels. A high TNF-α level was considered to be one of the bases of IR, which act by disturbing tyrosine phosphorylation of insulin receptor substrate (IRS)-1, a central molecule of the insulin-signaling cascade. Meanwhile, HCV directly causes liver steatosis. All the above events may precipitate the development of liver fibrosis. TNF-α system activation, liver steatosis and fibrosis contribute to the development of IR, which plays a pivotal role in the development of subsequent metabolic events [8]. Meanwhile, HCV-induced inflammatory changes may subsequently lead to increased oxidative stress and increased peroxidation, which evoke systemic inflammatory responses (SIR) more often than other liver diseases [20]. SIR triggered by HCV and/or its subsequent immune cascades and cytokine storms may play a major role in the related pathogenic mechanisms in terms of liver injury and the unique extrahepatic manifestations (Fig. 2). SIR may also contribute either directly or indirectly to the disease course, viral response, disease severity, and response to antiviral treatment. Cytokine triggering, which interacts with innate and/or adaptive immune responses, is one of the major concealed players of the scenario.

Evidence showing a direct diabetogenic effect of HCV per se came from previous experimental study showing that the ability of insulin to lower the plasma glucose level was impaired without gain in body weight at young age in HCV core gene transgenic mice. HCV core-induced suppressor of cytokine signalling 3 may promote proteosomal degradation of IRS1 and IRS2 through ubiquitination, which may be a unique mechanism of HCV-associated IR [21]. In a clinical observation, an increase in fasting insulin level was associated with the presence of serum HCV core protein, the severity of hepatic fibrosis, and a decrease in expression of IRS-1 and IRS-2 in patients with HCV infection. More severe IR was present in noncirrhotic patients with HCV infection than in patients with other liver diseases. In patients with undetectable levels of HCV core, fasting insulin levels were within the normal range. In contrast, in patients with detectable levels of HCV core, fasting insulin levels were increased [16]. Taken together, HCV core protein seems to play a pivotal role in HCV-associated IR. The precise mechanisms whereby HCV infection leads to IR and glucose abnormalities may differ from the usual pathogenesis of DM.

Figure 2. Possible pathogenic mechanisms leading to the development of insulin resistance and subsequent metabolic disorders. HCV triggers an immune cascade, mainly mediated by Th1 lymphocytes. These lymphocytes increase the activation of TNF-α and elevation of IL-6 levels. HCV directly leads to steatosis, particularly in those with genotype-3 infection. HCV may also induce systemic inflammatory response and cytokine storms, which are potentially fibrogenic factors. All the events increase the risk for IR. Fibrosis may be exacerbated by the development of IR, partly by the activation of hepatic stellate cell. IR plays a pivotal role in the development of subsequent metabolic events. With respect to the development of DM, pancreatic beta-cell hyperfunction aiming to maintain glucose homeostasis and elevated serum insulin level is the main feature before overt DM occurs. The scene of pancreatic beta-cell hyperfunction and beta-cell exhaustion may develop in the initial stages of HCV infection. The milieu of host factors (genetic predisposition, male, race, body mass index etc.), environmental factors (sedentary lifestyle, diet etc.) and viral factors (genotype, viral load) is also involved into the complex context. DM = diabetes mellitus; HCV = hepatitis C virus; IL-6 = interleukin-6; IR = insulin resistance; MS = metabolic syndrome; TNF-α = tumor necrosis factor-α.
T2DM in those with non-HCV liver diseases. HCV may induce IR regardless of the severity of liver disease and IR may be associated with severe hepatic fibrosis and contribute to fibrotic progression [13,22–25]. There was also a dose–response relationship between HCV RNA level and the presence of IR, whilst IR was positively associated with the severity of hepatic steatosis [26].

Clinical view

The role of the oral glucose tolerance test

T2DM is often present at least 4–7 years before diagnosis [27]. Therefore, definitive diagnosis of glucose abnormalities is an important issue because it allows attempts to improve clinical outcomes, such as weight reduction and lifestyle modification [28,29]. However, almost all T2DM patients have experienced the prediabetic condition (i.e., impaired fasting glucose level (IFG) and/or impaired glucose tolerance (IGT)) before a definite diagnosis of T2DM is made. In addition to future DM development, the prediabetic condition (IFG and IGT) also carries a risk for cardiovascular disease [30,31].

Generally and commonly, fasting plasma glucose (FPG) level alone is used as a screening test for the diagnosis of DM. However, this practice is based on the relative convenience and lower cost of FPG compared with a 75-g oral glucose tolerance test (OGTT) [32,33]. It was estimated that 19.3–59.3% of glucose abnormalities remained undetected using the current IFG criteria alone [34].

The same scenario exists in the link between glucose abnormalities and HCV infection. Previous data linking HCV infection and DM mainly focused on patients with overt DM. A threefold increase in the prevalence of glucose abnormalities was observed in anti-HCV(+) patients in comparison with anti-HCV(−) patients. In addition, 18% more new DM cases and 30% more new cases of IGT were uncovered by OGTT in anti-HCV(+) patients, which were significantly higher than those values in anti-HCV(−) patients [35]. Another more stringent case-control study from Taiwan recruited 683 CHC patients and 515 sex- and age-matched community-based controls. The prevalence of normoglycemia, IGT and T2DM in 683 CHC patients was 27.7%, 34.6%, and 37.8%, respectively. OGTT was performed in 522 CHC patients and 447 controls without known T2DM. Of note is that 19.3% of CHC patients who readily met with DM criteria were undiagnosed (Fig. 3). For those without known DM, there was a 3.5-fold increase in the prevalence of glucose abnormalities in CHC patients in comparison with controls (Table 1). Further analysis demonstrated that for those without known DM history, CHC patients had a higher risk of DM and IGT than controls with an odds ratio of 3.3. For those without known DM history and with normal FPG level, CHC patients had a higher risk of DM and IGT than controls with an odds ratio of 10.2 [36]. The studies implied that CHC patients carried a high prevalence of glucose abnormalities and also suggested that determination of glucose abnormalities by OGTT should be indicated. It might also be suggested that different criteria are necessary for DM diagnosis in patients with HCV infection, such as lower cutoff levels for normoglycemia, prediabetes and DM.

Glucose abnormalities affecting treatment efficacy of CHC

The “gold standard” for IR assessment is the hyperinsulinemic–euglycemic clamp test. However, the difficulty of the technique and its laborious nature much discourage the wider use of the test. The Homeostatic Model Assessment (HOMA), which has been used in large epidemiological studies, offers an estimate of IR. HOMA has the advantage of requiring only a single fasting plasma sample measured for glucose and insulin. Nonetheless, the lack of standardization of insulin assays and the difference of IR standardization between countries may undermine the accuracy of the measurements [37].

Combination therapy with pegylated IFN (PegIFN) and ribavirin (RBV) has been recommended as standard of care (SOC) for patients with HCV infection with favorable efficacy [38–40]. It therefore provides a wide scope of view addressing the correlation between HCV infection and IR. Several clinical predictors of the sustained virologic response (SVR) to combination therapy have been elucidated. The viral factors include genotypes, pretreatment viral load and on-treatment viral kinetics [38–40], whereas the host factors constitute age, BMI, races, interleukin-28B (IL-28B) polymorphisms etc. [40–42]. Glucose abnormalities have also been suggested recently to be a risk factor for nonresponse [43]. Patients with high HOMA-IR achieved a significantly lower rate of SVR than those who with low IR [43,44]. The significantly lower SVR rate in high HOMA-IR patients compared to low HOMA-IR patients was observed in G-1 patients but not in non-G-1 patients (Fig. 4). Of note was that IR was associated with SVR, especially among “difficult-to-treat” patients, i.e., the patients with G-1 infection and high pretreatment viral loads (>400,000 IU/ml). Since IR is considered as a factor which can be modified and improved by various interventions, further prospective studies will be valuable to evaluate whether the effective approaches to improve IR before initiation of the combination therapy for CHC can significantly increase the SVR rate.
Whether or not reducing IR using insulin-sensitizing agents improves treatment outcomes is speculative. Current data from clinical trials by adding pioglitazone or metformin to SOC have proved to be disappointing [45,46]. This may suggest that the emergence of IR in CHC evolved from the multifactorial, complex context encompassing viral, host and environmental factors.

**Treatment outcome affecting glucose abnormalities**

IFN has been used widely for CHC treatment for two decades [40,47]. However, IFN is an integral player in immunity and may exacerbate an existing autoimmune tendency, which may subsequently precipitate immune-mediated abnormalities [48]. Emergences of IR and subsequent DM have been demonstrated with IFN-based therapy, although the mechanism remains to be clarified [48,49]. Therefore, the interplay between IFN-based antiviral therapy and alteration of insulin sensitivity deserved to be elucidated. Reduced IR and subsequent improved glucose control after conventional IFN therapy was observed among chronic hepatitis B or CHC patients [50]. Romero-Gomez et al. showed that HOMA-IR decreased after treatment in responders, whilst it remained unchanged in nonresponders [46]. Kawaguchi et al. further demonstrated that clearance of HCV improves IR, beta-cell function, and hepatic IRS1/2 expression by immunostaining, whilst there were no significant changes in IR and beta-cell function after antiviral therapy in nonresponders and relapsers [51]. Recently, results of the HALT-C study which recruited patients with advanced fibrosis or more showed that on-treatment virological suppression correlated with reduction in HOMA-IR at Week 24 [52]. Huang et al. further extended the observation in G-1 and -2 patients showing that there was no significant decline of HOMA-IR even in responders. The significant decline of HOMA-IR after treatment was observed only in patients with high pretreatment HOMA-IR, regardless of SVR achievement [53]. Recent study in a clinical trial cohort of CHC patients showed that SVR was independently associated with a reduction in IR in G-1 but not G-2/3 patients. The results suggest a causal relationship between specific genotype and IR [15]. The somewhat discordant results may imply that the HOMA-IR with respect to SVR may have been influenced by variables such as race, age, genotypes, validation methods for diabetes, cut-off value of IR, treatment adherence, and/or the presence of liver steatosis. Since the mechanisms that are involved in the emergence of IR are multifarious, further long-term follow-up study is needed to elucidate them in this context.

In addition to hyperinsulinemia, pancreatic beta-cell hyperfunction aiming to maintain glucose homeostasis and elevated serum insulin level is the main feature of glucose abnormalities. The scene is also common in HCV infection, and insulin secretion is increased in the initial stages of HCV infection to compensate for IR development in both experimental and human studies. There was a significant relief of beta-cell function in nondiabetic Taiwanese CHC patients with adequate treatment adherence after PegIFN/RBV combination therapy, particularly in responders [51]. There was no significant decline of HOMA-IR in responders. The sequential change of beta-cell function might suggest that beta-cell function recovered earlier than that of IR in CHC patients receiving PegIFN/RBV combination therapy.

**Interaction with IL-28B genetic polymorphism**

Recently, studies based on genome-wide associated studies (GWAS) have shown that single nucleotide polymorphisms

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**Table 1** Characteristics of CHC patients without known DM and controls and their glucose abnormalities validated by OGTT.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Anti-HCV(−) controls</th>
<th>Anti-HCV(+) patients</th>
<th>p</th>
<th>Odds ratio, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>447</td>
<td>552</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50.5 ± 13.7</td>
<td>52.0 ± 12.4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>222 (49.7)</td>
<td>268 (48.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>289 (64.7)</td>
<td>189 (34.2)</td>
<td>&lt;0.001</td>
<td>0.29, 0.22–0.37</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>145 (32.4)</td>
<td>236 (42.8)</td>
<td>0.001</td>
<td>1.56, 1.20–2.02</td>
</tr>
<tr>
<td>Subclinical DM</td>
<td>13 (2.9)</td>
<td>127 (23.0)</td>
<td>&lt;0.001</td>
<td>9.98, 5.55–17.9</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± SD. CHC = chronic hepatitis C virus infection; DM = diabetes mellitus; OGTT = 75-g oral glucose tolerance test; CI = confidence interval; NS = not significant.
(SNPs) at and/or near the IL28B gene, which encodes interferon-\(\lambda\), play a critical role in the treatment efficacy of HCV infection [54,55]. It has been considered to be the most important host factor contributing to SVR. Therefore, the interplay between IL28B polymorphism and IR and its related outcomes after antiviral therapy in CHC patients deserves to be elucidated.

Recent studies demonstrated that there was no significant difference in IL28B genotype distribution according to pretreatment IR [56,57]. IR may undermine the advantages of a favorable IL28B polymorphism to achieve SVR in G-1 patients [57]. Huang et al. further confined the observation among prediabetic CHC patients with excellent treatment adherence whose hemoglobin A1c levels were 5.7–6.4%. There was no significant association between IL28B gene polymorphism and baseline IR across G-1 and -2 patients [56]. However, discordant results were recently reported from another European study showing that IR is more common in carriers of the unfavorable allele of IL28B in G-1 and -4 nondiabetic patients [58].

However, no significant association was observed between IL28B gene polymorphism and outcome of glucose abnormalities 24 weeks after completion of treatment (Fig. 5). Intriguingly, despite no statistical significance being reached, the prevalence of a favorable gene polymorphism in patients who developed DM after therapy tended to be lower than patients who remained as prediabetic and those who developed normoglycemia after therapy. The real scenario between gene polymorphism and IR in different phases of glucose abnormalities deserves to be further evaluated in a long-term fashion.

Future perspectives

Recently, direct-acting antiviral agents (DAA) are under investigation, including protease inhibitors, RNA polymerase inhibitors, and nonstructure protein 5A and 5B inhibitors. Currently, the triple therapy with the first-generation protease inhibitors (PI) and SOC can increase the SVR rates from 40% to 70% in naive patients, and from 20% to 65% in treatment-experienced patients with G-1 infection [59,60]. The emergence of DAA provides another window through which to view the interaction between CHC and IR. In a pilot Phase Ib placebo-controlled study, a cohort of treatment-naive G-1 patients received dano-previr, a PI, for 14 days. Serum HCV RNA was in a close parallel with HOMA-IR according to the pattern of virological response. Besides the proof of the efficacy of the new specific antiviral drugs to overcome IR, the results of this study thus provide definitive evidence for the link between HCV infection and IR [61].

Concordant findings from recent study demonstrated that baseline IR was not predictive of virological response in treatment-naive G-1 patients receiving another PI (telaprevir) plus PegIFN/RBV therapy. In addition, SVR was associated with improved IR. This implied that, in contrast with PegIFN/RBV, DAA may overcome the potential negative effect of metabolic factors and IR on treatment efficacy [61]. This growing evidence helps to elucidate the interaction between IR and CHC. It may also help to clarify the underlying pathogenic mechanisms leading to IR in HCV infection.

However, management of IR mainly depends on both pharmaceutical intervention and lifestyle modifications, such as exercise, diet control and weight reduction. Whether these interventions play a role in the disease course and prognosis of CHC patients deserves to be elucidated.

Conclusion

Glucose abnormalities are characteristic in patients with HCV infection. The development of IR leads to some impact on the disease activity, disease course, clinical outcomes, and treatment efficacy of current SOC. Enormous challenges for patient management have been raised in parallel with the occurrence of glucose abnormalities. The precise mechanisms which contribute to glucose abnormalities have not been fully clarified. Inspiring data and studies during past decades, however, have much enhanced our knowledge of this unique link between a viral hepatitis disease and a worldwide metabolic disorder. Particularly with the rapid progression of new therapies for CHC in recent years, the interaction between HCV infection and glucose abnormalities will likely become clearer. Meanwhile, recent promising data based on investigation of host epigenetics have greatly extended our understanding of the impact of host susceptibility on the occurrence of IR in CHC. Taken together, these recent advances shed great light for the future exploration of glucose abnormalities in HCV infection.

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References

Glucose abnormalities and HCV


