Kaohsiung Journal of Medical Sciences (2013) 29, 61–68

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.kjms-online.com

REVIEW ARTICLE

Glucose abnormalities in hepatitis C virus infection

Jee-Fu Huang [a,b], Ming-Lung Yu [b,c], Chia-Yen Dai [b,c], Wan-Long Chuang [b,c,*]

[a] *Department of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[b] *Faculty of Internal Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c] *Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*

Received 17 September 2012; accepted 20 November 2012
Available online 29 December 2012

KEYWORDS
Direct-acting antiviral agents;
Hepatitis C virus;
Insulin resistance;
Pegylated interferon;
Ribavirin

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.

* Corresponding author. Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100, Tzyou 1st Road, Kaohsiung City 807, Taiwan.
E-mail addresses: jf71218@gmail.com, waloch@kmu.edu.tw (W.-L. Chuang).

1607-551X/$36
http://dx.doi.org/10.1016/j.kjms.2012.11.001

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 over 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

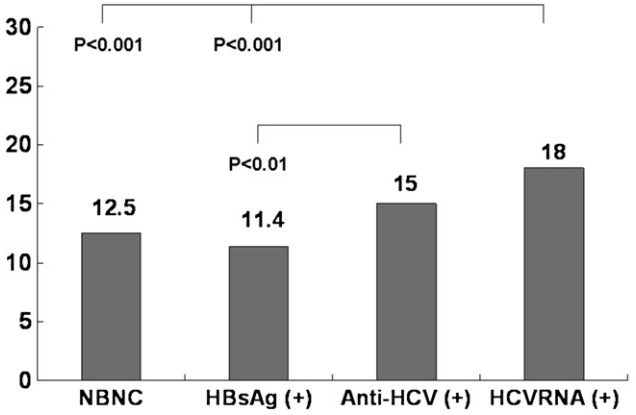

Figure 1. Prevalence of T2DM among patients with different etiologies of viral hepatitis. Anti-HCV = hepatitis C virus antibodies; HBsAg = hepatitis B surface antigen; HCVRNA = hepatitis C virus RNA; NBNC = neither HBsAg(+) nor anti-HCV(+); T2DM = type 2 diabetes mellitus.

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].

Pathophysiological 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

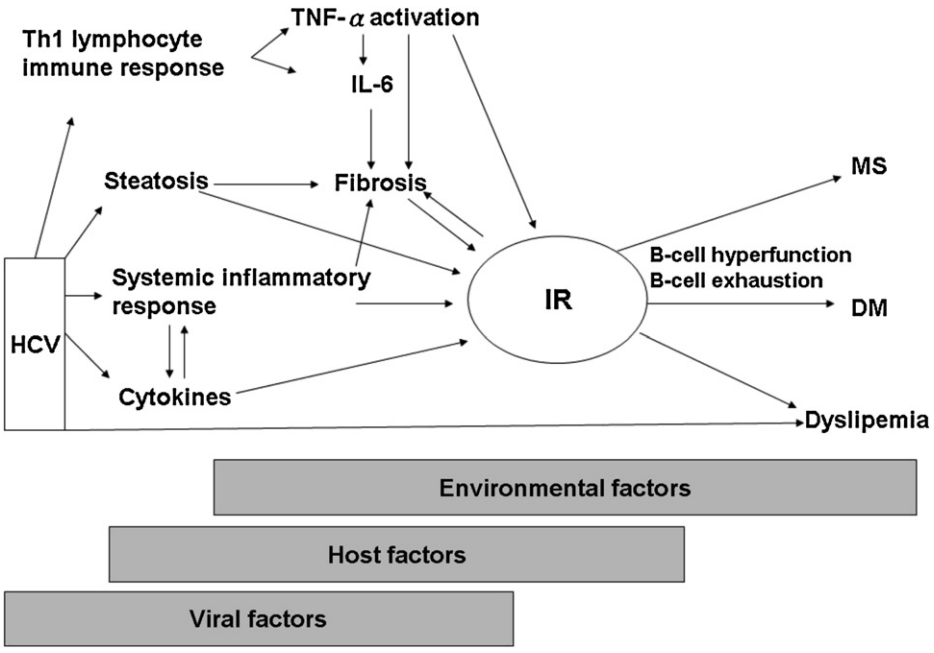

Figure 2. Possible pathogenic mechanisms leading to the development of insulin resistance and subsequent metabolic disorders. HCV triggers an immune cascade, mainly mediated by Th1 lymphocytes. These lymphocytes increase the activation of TNF-α and elevation of IL-6 levels. HCV directly leads to steatosis, 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 18.6% 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 cut-off levels for normoglycemia, prediabetes and DM.

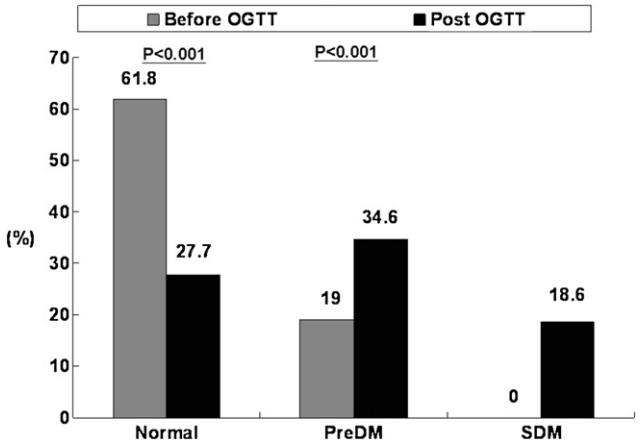

Figure 3. Distribution of glucose abnormalities among CHC patients before and after OGTT. CHC = chronic hepatitis C virus infection; OGTT = 75-g oral glucose tolerance test; PreDM = prediabetes; SDM = subclinical diabetes.

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.

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

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

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.

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.

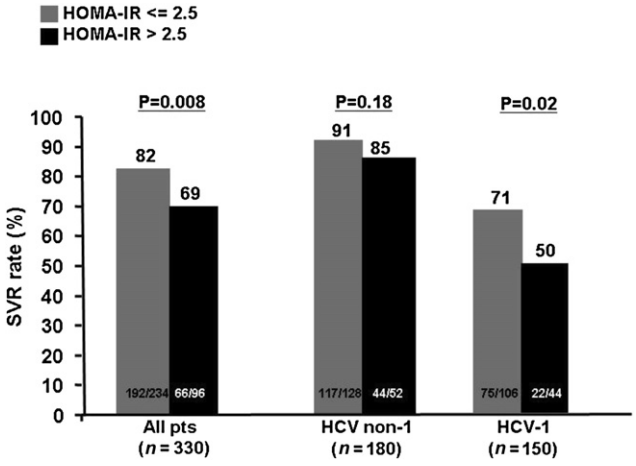

Figure 4. Sustained virological response rates to combination therapy with pegylated interferon-α and ribavirin among chronic hepatitis C patients and stratified by HCV genotype 1b and non-1b infection. The HOMA-IR was defined as high (>2.5 black bars) and low (62.5 white bars). HCV = hepatitis C virus; HOMA = homeostasis model assessment; IR = insulin resistance; SVR = sustained virological response.

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 [53]. 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

(SNPs) at and/or near the *IL28B* gene, which encodes interferon-λ, 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 A_{1c} 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 danoprevir, 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.

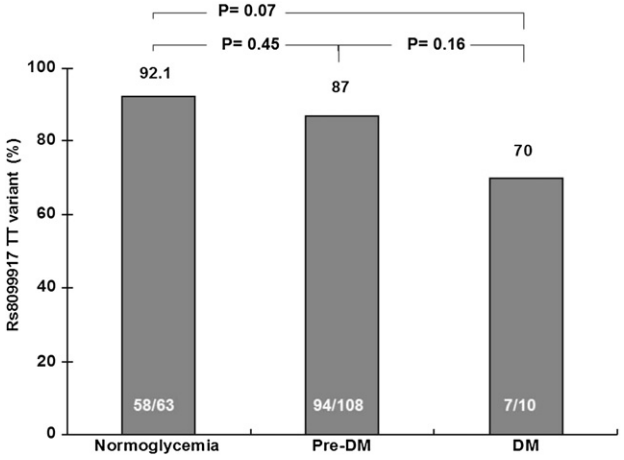

Figure 5. The proportion of IL28B rs8099917 TT genotype according to treatment outcomes of glucose metabolism in prediabetic chronic hepatitis C patients. IL28B = interleukin 28B.

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.

Acknowledgments

The authors thank the Taiwan Liver Research Foundation (TLRF) for secretarial help.

References

[1] Allison ME, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. J Hepatol 1994;21:1135—9.

[2] 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 Clin Proc 2000;75: 355—9.
[3] Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;29:328—33.
[4] Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Ann Intern Med 2000;133:592—9.
[5] Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrik J, et al. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. Hepatol 1999;30:1059—63.
[6] Antonelli A, Ferri C, Fallahi P, Pampana A, Ferrari SM, Goglia F, et al. Hepatitis C virus infection: evidence for an association with type 2 diabetes. Diabetes Care 2005;28:2548—50.
[7] Mehta SH, Brancati FL, Strathdee SA, Pankow JS, Netski D, Coresh J, et al. Hepatitis C virus infection and incident type 2 diabetes. Hepatol 2003;38:50—6.
[8] Lecube A, Hernandez C, Genesca J, Simo R. Glucose abnormalities in patients with hepatitis C virus infection: epidemiology and pathogenesis. Diabetes Care 2006;29:1140—9.
[9] Zein CO, Levy C, Basu A, Zein NN. Chronic hepatitis C and type II diabetes mellitus: a prospective cross-sectional study. Am J Gastroenterol 2005;100:48—55.
[10] Huang JF, Dai CY, Hwang SJ, Ho CK, Hsiao PJ, Hsieh MY, et al. Hepatitis C viremia increases the association with type 2 diabetes mellitus in a hepatitis B and C endemic area: an epidemiological link with virological implication. Am J Gastroenterol 2007;102:1237—43.
[11] Wang CS, Wang ST, Yao WJ, Chang TT, Chou P. Hepatitis C virus infection and the development of type 2 diabetes in a community-based longitudinal study. Am J Epidemiol 2007; 166:196—203.
[12] Wang CS, Wang ST, Yao WJ, Chang TT, Chou P. Community-based study of hepatitis C virus infection and type 2 diabetes: an association affected by age and hepatitis severity status. Am J Epidemiol 2003;158:1154—60.
[13] Petit JM, Bour JB, Galland-Jos C, Minello A, Verges B, Guiguet M, et al. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. J Hepatol 2001;35:279—83.
[14] Zignego AL, Ferri C, Giannini C, Monti M, La Civita L, Careccia G, et al. Hepatitis C virus genotype analysis in patients with type II mixed cryoglobulinemia. Ann Intern Med 1996;124:31—4.
[15] 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;61:128—34.
[16] 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. Am J Pathol 2004;165:1499—508.
[17] Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001;414:799—806.
[18] Huang JF, Yu ML, Dai CY, Chuang WL, Chang WY. Metabolic aspects of hepatitis C virus infection. In: Moses P, editor. Molecular virology. 1st ed. Rijeka: Adoga; 2012. p. 33—62.
[19] Hadziyannis SJ. The spectrum of extrahepatic manifestations in hepatitis C virus infection. J Viral Hepat 1997;4:9—28.
[20] Lecube A, Hernandez C, Genesca J, Simo R. Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients: a case-control study. Diabetes Care 2006; 29:1096—101.
[21] 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. Gastroenterol 2004;126:840—8.
[22] Dai CY, Chuang WL, Ho CK, Hsieh MY, Huang JF, Lee LP, et al. Associations between hepatitis C viremia and low serum triglyceride and cholesterol levels: a community-based study. J Hepatol 2008;49:9—16.
[23] Taura N, Ichikawa T, Hamasaki K, Nakao K, Nishimura D, Goto T, et al. Association between liver fibrosis and insulin sensitivity in chronic hepatitis C patients. Am J Gastroenterol 2006;101:2752—9.
[24] 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. Gastroenterol 2003;125: 1695—704.
[25] Alexander GJ. An association between hepatitis C virus infection and type 2 diabetes mellitus: what is the connection? Ann Intern Med 2000;133:650—2.
[26] Hsu CS, Liu CJ, Liu CH, Wang CC, Chen CL, Lai MY, et al. High hepatitis C viral load is associated with insulin resistance in patients with chronic hepatitis C. Liver Int 2008;28:271—7.
[27] Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4—7 yr before clinical diagnosis. Diabetes Care 1992;15:815—9.
[28] Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368: 1096—105.
[29] Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343—50.
[30] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33:S62—9.
[31] Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. Diabetes Care 1979;2:120—6.
[32] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735—52.
[33] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393—403.
[34] Hung WW, Chang CJ, Lee YJ, Hsin SC, Lin KD, Hsieh MC, et al. Metabolic risk factors in southern Taiwanese with impaired fasting glucose of 100 to 109 mg/dL. Metabolism 2007;56: 528—32.
[35] Lecube A, Hernandez C, Genesca J, Esteban JI, Jardi R, Simo R. High prevalence of glucose abnormalities in patients with hepatitis C virus infection: a multivariate analysis considering the liver injury. Diabetes Care 2004;27:1171—5.
[36] Huang JF, Yu ML, Dai CY, Hsieh MY, Hwang SJ, Hsiao PJ, et al. Reappraisal of the characteristics of glucose abnormalities in patients with chronic hepatitis C infection. Am J Gastroenterol 2008;103:1933—40.
[37] Neuschwander-Tetri BA. Hepatitis C virus-induced insulin resistance: not all genotypes are the same. Gastroenterol 2008;134:619—22.
[38] Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. Hepatol 2004;39: 1147—71.
[39] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales Jr FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347: 975—82.

[40] Yu ML, Chuang WL. Treatment of chronic hepatitis C in Asia: when East meets West. J Gastroenterol Hepatol 2009;24:336—45.
[41] Svegliati-Baroni G, Bugianesi E, Bouserhal T, Marini F, Ridolfi F, Tarsetti F, et al. Post-load insulin resistance is an independent predictor of hepatic fibrosis in virus C chronic hepatitis and in non-alcoholic fatty liver disease. Gut 2007;56:1296—301.
[42] Yu ML, Huang CF, Huang JF, Chang NC, Yang JF, Lin ZY, et al. Role of interleukin-28B polymorphisms in the treatment of hepatitis C virus genotype 2 infection in Asian patients. Hepatol 2011;53:7—13.
[43] Romero-Gomez M, Del Mar Viloria M, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Gastroenterol 2005;128: 636—41.
[44] Dai CY, Huang JF, Hsieh MY, Hou NJ, Lin ZY, Chen SC, et al. Insulin resistance predicts response to peginterferon-alpha/ribavirin combination therapy in chronic hepatitis C patients. J Hepatol 2009;50:712—8.
[45] Overbeck K, Genne D, Golay A, Negro F. Pioglitazone in chronic hepatitis C not responding to pegylated interferon-alpha and ribavirin. J Hepatol 2008;49:295—8.
[46] Romero-Gomez M, Diago M, Andrade RJ, Calleja JL, Salmeron J, Fernandez-Rodriguez CM, et al. Treatment of insulin resistance with metformin in naive genotype 1 chronic hepatitis C patients receiving peginterferon alfa-2a plus ribavirin. Hepatol 2009;50:1702—8.
[47] Yu ML, Dai CY, Huang JF, Chiu CF, Yang YH, Hou NJ, et al. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. Hepatol 2008;47:1884—93.
[48] Borg FA, Isenberg DA. Syndromes and complications of interferon therapy. Curr Opin Rheumatol 2007;19:61—6.
[49] Chedin P, Cahen-Varsaux J, Boyer N. Non-insulin-dependent diabetes mellitus developing during interferon-alpha therapy for chronic hepatitis C. Ann Intern Med 1996;125:521.
[50] Tai TY, Lu JY, Chen CL, Lai MY, Chen PJ, Kao JH, et al. Interferon-alpha reduces insulin resistance and beta-cell secretion in responders among patients with chronic hepatitis B and C. J Endocrinol 2003;178:457—65.
[51] 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. Am J Gastroenterol 2007;102:570—6.
[52] 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. Clin Gastroenterol Hepatol 2010;8:458—62.
[53] Huang JF, Dai CY, Yu ML, Huang CF, Huang CI, Yeh ML, et al. Pegylated interferon plus ribavirin therapy improves pancreatic beta-cell function in chronic hepatitis C patients. Liver Int 2012;32:962—9.
[54] Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461: 399—401.
[55] Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009;41:1105—9.
[56] Huang JF, Yu ML, Huang CF, Juo SH, Dai CY, Hsieh MY, et al. The outcomes of glucose abnormalities in pre-diabetic chronic hepatitis C patients receiving peginterferon plus ribavirin therapy. Liver Int 2012;32:962—9.
[57] Ogawa E, Furusyo N, Murata M, Ikezaki H, Ihara T, Hayashi T, et al. Insulin resistance undermines the advantages of IL28B polymorphism in the pegylated interferon alpha-2b and ribavirin treatment of chronic hepatitis C patients with genotype 1. J Hepatol 2012;57:534—40.
[58] Stattermayer AF, Rutter K, Beinhardt S, Scherzer TM, Stadlmayr A, Hofer H, et al. Association of the IL28B genotype with insulin resistance in patients with chronic hepatitis C. J Hepatol 2012;57:492—8.
[59] Pearlman BL. Protease inhibitors for the treatment of chronic hepatitis C genotype-1 infection: the new standard of care. Lancet Inf Dis 2012;12:717—28.
[60] Dusheiko G, Wedemeyer H. New protease inhibitors and direct-acting antivirals for hepatitis C: interferon's long goodbye. Gut 2012;61:1647—52.
[61] Serfaty L, Forns X, Goeser T, Ferenci P, Nevens F, Carosi G, et al. Insulin resistance and response to telaprevir plus peginterferon alpha and ribavirin in treatment-naive patients infected with HCV genotype 1. Gut 2012;61: 1473—80.