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Metabolic Aspects of Hepatitis C Virus Infection

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1. Introduction

Hepatitis C virus (HCV) infection is one of the most important causes of cirrhosis and hepatocellular carcinoma (HCC) and has a tremendous impact on public health worldwide. It is estimated that there are more than 170 million people chronically infected with HCV, and 3 to 4 million persons are newly infected annually. The risk for developing cirrhosis 20 years after initial HCV infection among those chronically infected varies between studies, but is estimated at around 10%–15% for men and 1–5% for women. Once cirrhosis is established, the rate of developing HCC is at 1%–4% per year. Approximately 280,000 deaths per year are related to HCV infection. HCV-related end-stage liver disease and HCC have become the leading cause for liver transplantation globally.

HCV *per se* is both hepatotropic and lymphotropic. Replication of HCV in diseased extrahepatic organs and tissues may have cytopathic effects. It, therefore, may either trigger latent autoimmunity or induce an autoimmune disease *de novo*. The concise context of pathogenic mechanisms is complex and remains to be elucidated. Generally, in addition to established liver injury, there are multiple examples of extrahepatic metabolic disorders attributed to HCV infection, such as type 2 diabetes mellitus (T2DM), thyroiditis, glomerulopathy, mixed cryoglobulinemia, and other immunological abnormalities. These disorders possess some extent of impact on the disease activity, disease course, clinical outcomes, and treatment efficacy of current therapy.

The aims of this chapter initially reviewed recent studies in terms of the metabolic manifestations of chronic HCV infection (CHC), e.g. proteinuria, T2DM, lipid abnormalities and metabolic syndrome to elucidate the characteristics of metabolic abnormalities and their clinical relevants from the aspect of epidemiological view.

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Secondly, robust epidemiological data demonstrated the mutual link between HCV infection and T2DM. HCV plays a direct pathogenic role in the emergence of T2DM even in the early stage of liver histological changes and its diabetogenic role has been confirmed. Although the precise mechanisms whereby HCV infection leads to insulin resistance (IR) and glucose abnormalities are not fully clear, it differs from the usual pathogenesis of T2DM in those with non-HCV liver diseases. This chapter also tried to clarify 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 interesting suite.

Liver has long been regarded as the key player manipulating complex biochemical metabolism which is essential to maintenance of homeostasis. Recently, studies regarding cytokines have been prevailing worldwide in the past decade. We also introduced several translational studies aiming to elucidate the specific roles of the newcomers in a clinical setting. It will be helpful to clarify the host viral interaction and possible pathogenic mechanisms of this topic.

2. The epidemiological links

2.1 Nephropathy

Viral hepatitis infection *per se* may lead to nephropathy. This uncommon extrahepatic manifestation might be induced either by direct cytopathic effect of virus or interplay between viral, host and environmental factors (Congia et al., 1996; Mazzaro et al., 2000; Strassburg, et al., 1996). The association between hepatitis B virus (HBV) infection and renal involvement, mainly membranous nephropathy, was first reported in 1971 (Combes et al., 1971). Deposition of Australia antigen-antibody complexes in glomerular basement membrane was identified in renal tissue of glomerulonephritis. Since then many reports have been made suggesting the association between HBV infection and nephropathy (Johnson et al., 1990; Levo et al., 1977). However, the natural history and the pathogenesis are not well understood but are believed to be mediated by deposition of immune complexes of HBV antigens in the glomeruli (Ito et al., 1981).

On the other side, hepatitis C virus (HCV) has been shown to be a lymphotropic as well as a hepatotropic virus (Mazzaro et al., 2000). Replication of HCV in diseased extrahepatic organs and tissues may have cytopathic effects. It, therefore, may either trigger latent autoimmunity or induce *de novo* an autoimmune disease (Hadziyannis, 1997). HCV-associated nephropathy has been postulated to be a distinct extrahepatic manifestation, which might be related to interplay between intrinsic renal disease, autoimmune abnormality, and host susceptibility (Congia et al., 1996; Garini et al., 2005; Meyers et al., 2003). It occurs largely in the context of cryoglobulinemia (Garini et al., 2005). There are also quite a number of cases who do not have cryoglobulinemia but still present with one of the major HCV-associated nephropathy namely membranoproliferative glomerulonephritis, membranous nephropathy, and focal segmental glomerulosclerosis, the latter two generally not associated with cryoglobulinemia (Meyers et al., 2003). Barsoum et al suggested that in addition to a renal microstructure suitable for sieving out macromolecules associated with HCV infection, such as cryoglobulins and immune complexes, there are several circumstances in which renal cells may be a target for viral cytopathic effects. These effects include ingredients for HCV attachment, endocytosis, and entry. Upregulation of Toll-like

receptors and metalloproteinases in mesangial inflammation when there is HCV infection may induce injury through an aggravated immune response. HCV also can enter cells and replicate in B lymphocytes, and it is associated with AA amyloidosis in class VI schistosomal glomerulopathy (Lee et al., 2010). HCV-associated glomerulonephritis, together with interstitial tubular injury, may cause the subsequent CKD.

Previous studies have shown that in persons with HCV infection, higher incidence of microalbuminuria and proteinuria did occur in CHC patients than in those with other forms of liver disease (Liangpunsakul et al., 2005; Muramatsu et al., 2000). Liangpunsakul et al conducted the first nested case-control study to examine the association between microalbuminuria and HCV infection by using the Third National Health and Nutrition Examination Survey (NHANES III) database. The prevalence of microalbuminuria in patients with HCV infection was 12.4%, which was significantly higher than in controls (7.5%) ($P=0.001$). This difference persisted even after excluding diabetics from the analysis (11.4% vs. 6.7%) ($P=0.001$). In nondiabetic persons with HCV infection, microalbuminuria occurs more often in those who aged 20 years or more (Liangpunsakul et al., 2005).

Proteinuria has been shown to be an early diagnostic marker of kidney damage, and can predict the progression of renal disease in patients with diabetes as well as cardiovascular morbidity and mortality in diabetic and general population (Diercks et al., 2002). During the past decade, proteinuria has taken on a new importance, and is shown to be a cardinal sign and an independent risk factor for the outcome of both kidney and cardiovascular disease (Diercks et al., 2002). Not only is proteinuria associated with glomerular injury and loss of its normal permselective properties, but experimental data have demonstrated that protein-tubular cell interactions have inflammatory and fibrogenic consequences that can contribute to interstitial damage and fibrosis (Keane, 2000).

Two large-scale community studies have been conducted in 2 different HCV-endemic areas in Taiwan. Taiwan is a country prevalent for HBV infection and several scattered hyperendemic areas for HCV infection have been discovered in the past decades. The unique background thus provides a better scope of view to assess the difference of association with nephropathy between HBV and HCV infections. Lee et al recruited 54,966 adults in a county endemic for both HBV (9.9%) and HCV (9.4%) infections. There was a significant increasing trend of HCV seropositivity in parallel with CKD stages, ranging from 8.5% in stage 1 to 14.5% in CKD stages 4-5 (Figure 1) (Lee et al., 2010).

Huang et al also conducted a prospective community-based study enrolling 10,975 subjects to compare the prevalence of proteinuria among adult population in another HBV (13.1%) and HCV (6.5%) endemic area of southern Taiwan (Yang et al., 2006; Yu et al., 2001; Yu et al., 2001; Huang et al., 2006). Setting proteinuria as urine dipstick test $\geq 1+$, the prevalence of proteinuria among subjects seropositive for anti-HCV was significantly higher than HBV carriers and those negative controls. The prevalence of HCV infection was significantly higher among proteinuria than that of non-proteinuria individuals. Multivariate logistic regression analyses showed HCV infection was an independent significant factor associated with proteinuria. The significance remained even excluding those diabetics. By contrast, HBV infection did not show significant difference between proteinuria and non-proteinuria subjects. The robust epidemiological data demonstrated the consistent and significant association between HCV infection with both CKD prevalence and CKD disease severity.

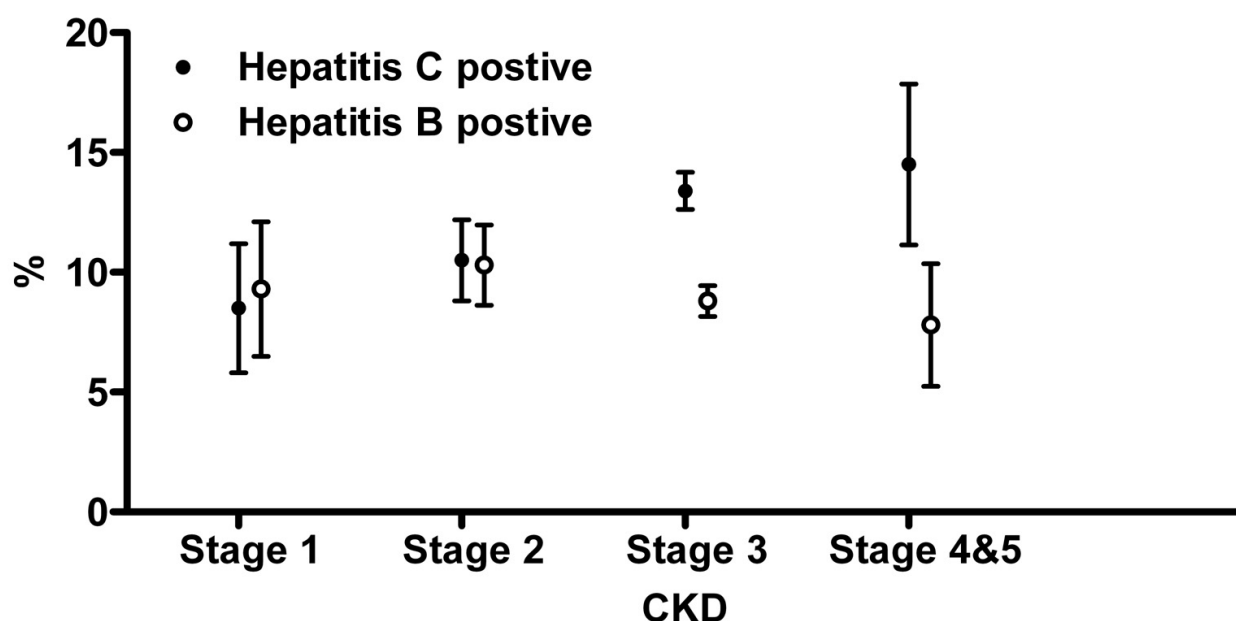


Fig. 1. Prevalence of hepatitis C virus infection and hepatitis B virus infection based on the staging of chronic kidney disease (CKD). Error bars represent 95% confidence intervals.

2.2 Type 2 diabetes mellitus

HCV infection and Type 2 diabetes mellitus (T2DM) are two major rising epidemics harboring tough challenges both to the clinicians and to the health-care systems in terms of diagnostic, therapeutic, and economic implications (Aytaman et al., 2008). In 2003, there were over 194 million people diagnosed with diabetes worldwide, with an estimated 333 million persons to be afflicted by 2025. These numbers, however, do not include those with undiagnosed diabetes, a population that is currently estimated to represent over 26% of the U.S. population alone. On the other side, HCV infection currently affects 3% of the world population, estimated 170 million people worldwide, leading to a substantial rise in the prevalence of chronic liver disease, with its enormous health and economic impacts. Although type 1 DM has been observed in patients treated with interferon (IFN), the majority of HCV-related diabetes is T2DM.

T2DM is a common endocrine disorder encompassing multifactorial pathogenetic 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 (Saltiel 2001). Although the precise mechanisms whereby these factors interact to produce glucose abnormalities are uncertain, it has been suggested that the final common pathway responsible for the development of T2DM is the failure of the pancreatic beta-cells to compensate for the insulin resistance (IR). The biological mechanism underlying IR or T2DM in HCV infection remains unclear. Shintani et al demonstrated 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 study. A high

level of tumor necrosis factor- α 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. These findings provided a direct experimental evidence for the contribution of HCV in the development of IR and in the pathogenesis of T2DM (Shintani et al., 2004). In addition, clinical study by Kawaguchi et al indicated an increase in fasting insulin levels 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 (Kawaguchi et al., 2004). HCV core-induced suppressor of cytokine signalling 3 may promote proteosomal degradation of IRS1 and IRS2 through ubiquitination, and which may be a unique mechanism of HCV-associated IR. In patients with undetectable levels of HCV core protein, fasting insulin levels were within the normal range. In contrast, in patients with detectable levels of HCV core protein, fasting insulin levels were increased. Thus, HCV core protein seemed to play a crucial role in HCV-associated IR.

There are strong evidence supporting an epidemiologic link between CHC and T2DM (Allison et al., 1994; Mason et al., 1999; Mehta et al., 2000; Wang et al., 2003; Zein et al., 2005). The association between T2DM and CHC was first reported 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 (Allison et al., 1994). 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(+) diabetics (Knobler et al., 2000). The prevalence of T2DM and impaired fasting glucose (IFG) was higher among HCV-infected patients with advanced versus those with early histological disease. Advanced histological disease predicted T2DM/IFG after controlling for other identified risk factors for T2DM (Zein et al., 2005). Similar features were also observed from Asia Pacific region. Huang et al, in a community survey 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 (Figure 2). It may imply that a persistent and/or active phase of HCV infection is associated with T2DM (Huang et al., 2007). Wang et al prospectively followed 4,958 persons aged 40 years or more without T2DM from a community-wide cohort in southern Taiwan for 7 years. The 7-year cumulative incidence of those anti-HCV+ subjects was nearly 2-folds increase than those HBsAg+ and negative controls. After stratification by age and body mass index (BMI), the risk ratio for T2DM in anti-HCV+ participants increased when age decreased and BMI levels increased (Wang et al., 2007). Generally, the prevalence of anti-HCV seropositivity in the T2DM population ranged from 1.8 to 12.1%, whereas T2DM developed in 14.5 to 33.0% of CHC patients (Allison et al., 1994; Antonelli et al., 2005; Caronia et al., 1999; Lecube et al., 2006; Mason et al., 1999; Mehta et al., 2003; Mehta et al., 2000; Zein et al., 2005). Different background in terms of ethnicity, age, prevalence of T2DM, BMI, viral load and genotype might contribute to the divergent results of the epidemiological observations. With respect to epidemiological aspect, HCV is considered to be diabetogenic and T2DM represented one more disease to be included in the list of established extrahepatic manifestations of HCV infection.

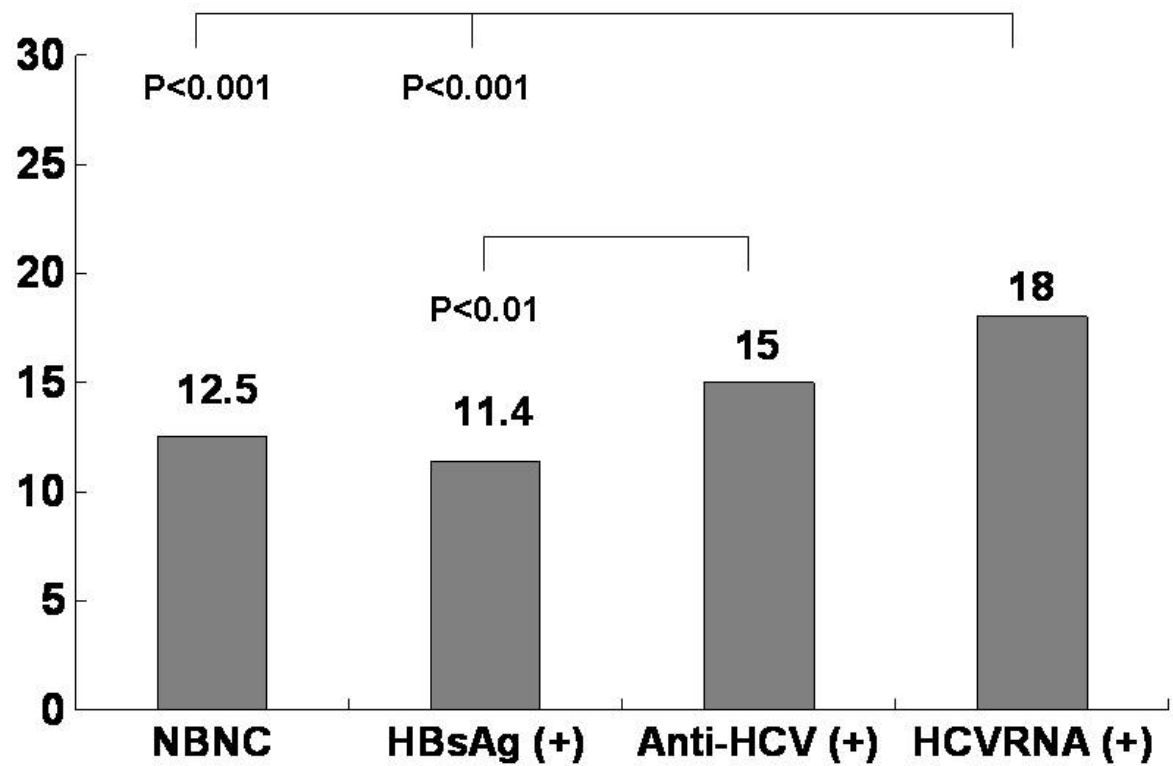


Fig. 2. Prevalence of T2DM among subjects with different etiologies of viral hepatitis. HBsAg: hepatitis B surface antigen; anti-HCV: hepatitis C virus antibodies; NBNC: neither HBsAg (+) nor anti-HCV (+); HCVRNA: hepatitis C virus RNA.

The relationship between T2DM and HCV genotypes remains controversial (Knobler et al., 2000; Lecube et al., 2006; Mason et al., 1999; Petit et al., 2001). Zignego et al demonstrated that HCV genotype-2a (G-2a) was specifically linked with extrahepatic manifestations such as cryoglobulinemia (Zignego et al., 1996). An association between G-2a infection and T2DM was also reported (Mason et al., 1999). However, no association was found between fasting insulin levels and HCV genotypes in Japanese study (Kawaguchi et al., 2004). Taiwanese study showed that neither HCV G-1 nor G-2 infection was significantly associated with T2DM (Huang et al., 2007). Recently a large-scale international collaborative study 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 in those 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 (Thompson et al., 2011).

2.3 Metabolic disorders

Although the precise mechanisms leading to HCV cell entry are not fully elucidated, HCV uptake by hepatocytes has been demonstrated to be mediated by the low-density lipoprotein (LDL) receptor as well as other proteins such as tetraspanin CD81, claudin-1 and occludin. Experiments in vitro showed competitive inhibition of binding between HCV and LDL-receptor by LDL-C (Monazahian et al., 1999). HCV cell entry is also mediated by another lipoprotein receptor, the scavenger receptor class B type I, which is responsible for

the entry of various classes of lipoproteins, primarily the high-density lipoproteins (HDL) (Negro, 2010). In addition, lipoproteins play an important role in the process of HCV infection since complexing of the virus to the low-density lipoprotein (VLDL-C) or LDL-C could promote endocytosis of HCV via the LDL receptor (Agnello et al., 1999). HCV infection and hypobetalipoproteinemia is characteristic in patients with HCV infection (Monazahian et al., 1999; Monazahian et al., 2000; Perlemuter et al., 2002). There are a lower cholesterol (total cholesterol, HDL-C and LDL-C) and a lower triglycerides (TG) levels in CHC patients than those of normal subjects (Dai et al., 2008; Siagris et al., 2006). Dai et al conducted a community-based mass-screening of 11,239 adults showing the subjects with normal serum cholesterol and TG levels had significantly higher proportion of anti-HCV+ than those who had elevated serum cholesterol and/or elevated TG levels. For anti-HCV+ patients, patients with normal serum cholesterol and TG levels had significantly higher proportion of positive HCV RNA than those who had elevated serum cholesterol and/or elevated TG levels. It is particularly noteworthy that subjects with HCV viremia have significantly lower serum cholesterol and TG levels than those who were negative for HCV RNA (Dai et al., 2008). Furthermore, a HCV genotype-based different impact on the lipid profile and hepatic steatosis was reported as well (Moriya et al., 2003; Serfaty et al., 2001). These epidemiological findings imply that HCV plays a significant role on serum lipid profiles and lipids are essential to the HCV life cycle. Therefore, alteration of blood lipids is a characteristic feature of HCV infection clinically. Recent studies demonstrated that successful eradication of HCV infection was associated with a significant increase in total cholesterol, LDL-C and TG levels in G-1, -2, and -3 infection (Tada et al., 2009). This increase from baseline was most pronounced in patients with G-3 infection (Thompson et al., 2011).

Metabolic syndrome (MS) is a complicated disorder encompassing clinical features of obesity, hyperglycemia, hypertension, dyslipidemia and IR. It carries a high risk for future development of micro- and macrovascular complications. Atherosclerosis and T2DM, as major subsequent events of MS, are critical health issues globally (Grundy et al., 2005). There is groundswell evidence indicating that the atherosclerotic process is regulated by intervening inflammatory mechanisms. IR, heroine of the scenario in the pathogenesis of MS, has been increasingly recognized as playing a key role in the inflammatory processes. Histologically, hepatic steatosis is a common feature of CHC, which is observed in 30-70% of the patients (Hsieh et al., 2007; Watanabe et al., 2008). Many factors are known to be risks for hepatic steatosis, including DM, hyperlipidemia, and obesity (Sanyal, 2005). Apart from its hepatotropic characteristic, HCV infection carries a significant pathogenic effect for development of IR, albeit the underlying biological mechanisms are diverse and multifactorial. Metabolic abnormalities including liver steatosis, obesity and DM can also worsen the course of CHC (Moucari et al., 2007; Tarantino et al., 2006).

The prevalence of the MS in patients with CHC varied from 4.4% in Italy, 24.7% in Taiwan and 51% in US veterans (Huang et al., 2009a; Keane et al., 2009; Svegliati-Baroni et al., 2007), suggesting that host factors such as ethnic origin could play a role in the association between IR and CHC (Conjeevaram et al., 2007; Serste et al., 2010). Liangpunsakul et al examined the relationship between nondiabetic subjects with HCV infection and microalbuminuria by using NHANES III database which consisted of 15,336 adults from the United States. There was no difference in the MS prevalence between HCV group and controls (Liangpunsakul et al., 2005). However, subjects with HCV infection carrying a

higher prevalence of MS than controls was observed from an HCV-hyperendemic area (>35% of anti-HCV+ prevalence in adults) in Taiwan. Those anti-HCV+ residents had a higher waist circumference and a higher prevalence of hypertension as the common features of MS (Huang et al., 2009). Further exploration is needed to clarify the complex context of MS with respect to different ethnicity. Furthermore, emerging lines of clinical data revealed that several metabolic disturbance; such as obesity, IR, and hepatic steatosis, are significant risk factors for decreased treatment response to pegylated IFN (PegIFN) and ribavirin combination therapy in CHC patients (Bressler et al., 2003; Camma et al., 2006; Romero-Gomez et al., 2005; Watanabe et al., 2008). The association between HCV infection and MS could be validated by the sequential changes of MS characteristics upon treatment response to antiviral therapy. In addition, the difference of atherosclerotic cardiovascular disease risk between MS subjects with HCV infection and non-HCV subjects deserves to be further elucidated.

3. Hepatitis C virus infection and type 2 diabetes mellitus

3.1 The characteristics of glucose abnormalities in patients with chronic hepatitis C infection

There has been emerging and robust data, particularly in the aspect of epidemiology, suggesting that a higher prevalence of T2DM among patients with HCV infection, whereas HCV infection is a risk factor for developing T2DM.

T2DM is often present at least 4 to 7 years before diagnosis (Harris et al., 1992). 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 (Gerstein et al., 2006; Tuomilehto et al., 2001). On the other side, almost all T2DM patients have experienced the prediabetic condition, namely, IFG and/or impaired glucose tolerance (IGT), before a definite diagnosis of T2DM was made. In addition to future DM development, the prediabetic condition also carries a risk for cardiovascular disease (Kannel et al., 1979). 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-gram oral glucose tolerance test (OGTT) (Grundy et al., 2005; Knowler et al., 2002). The discrepancy of distribution of glucose abnormalities before and after OGTT was estimated that 19.3–59.3% of glucose abnormalities remained undetected using the current IFG criteria alone (Huang et al., 1999; 2003).

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. Lecube et al prospectively recruited a total of 642 hispanic patients (498 anti-HCV+ and 144 anti-HCV-) in a single center. Patients were classified as having chronic hepatitis (n = 472) or cirrhosis (n = 170) by means of clinical manifestations or liver biopsy. A 3 folds increase in the prevalence of glucose abnormalities was observed in HCV+ patients with chronic hepatitis in comparison with HCV- subjects (32% vs. 12%). 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 (Lecube et al., 2004). Another case-control study recruited 683 CHC patients and 515 sex-/ age-matched

community-based controls were conducted in Taiwan aiming to elucidate the entire suite of glucose abnormalities. OGTT was performed in 522 CHC patients and 447 controls without known T2DM. The prevalence of normoglycemia, IGT, and T2DM in 683 CHC patients was 27.7%, 34.6%, and 37.8%, respectively. Of note is 18.6% of CHC patients who readily met with DM criteria were undiagnosed (Figure 3). For those without known DM, there were 3.5 folds increase in the prevalence of glucose abnormalities in CHC patients in comparison with controls (Huang et al., 2008) (Table 1). The two 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 in CHC patients. It might also suggest that different criteria are necessary for DM diagnosis in patients with HCV infection, such as a lower cut-off for normoglycemia, prediabetes, and DM.

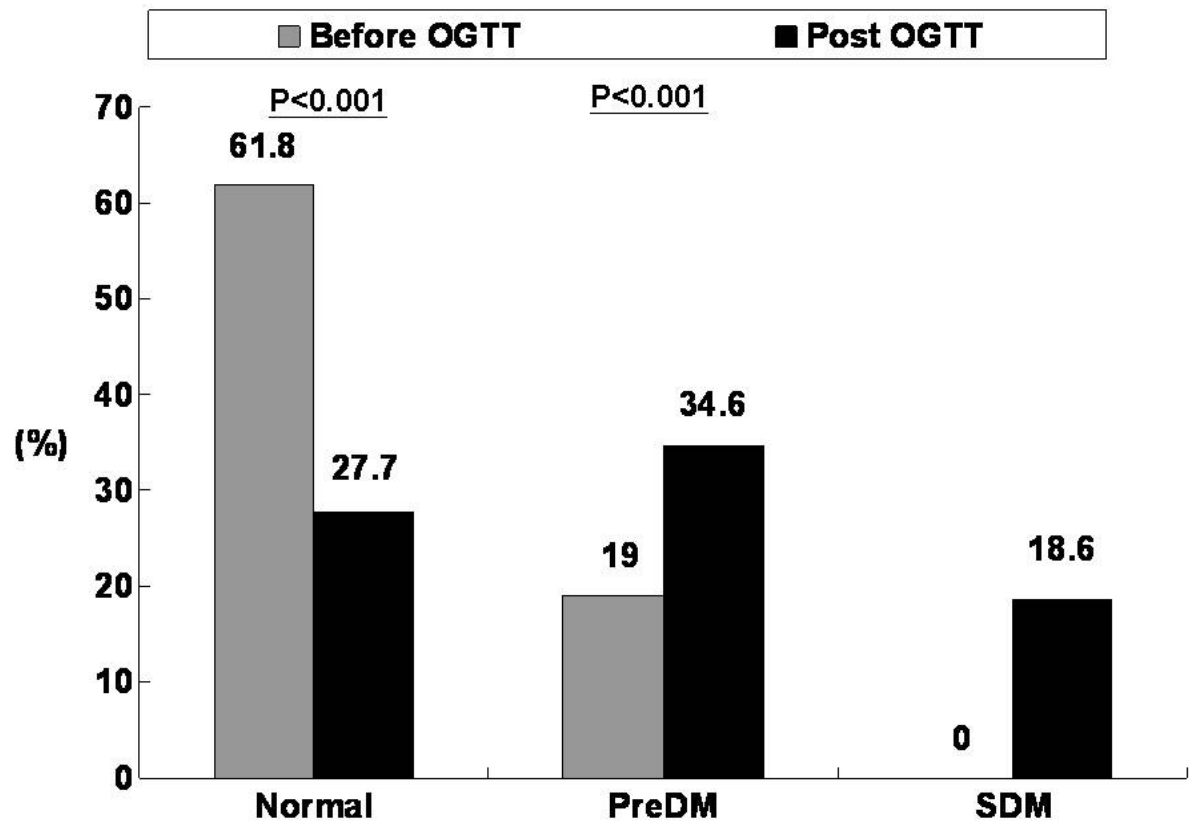


Fig. 3. Distribution of glucose abnormalities among CHC patients before and after OGTT. OGTT: 75-g oral glucose tolerance test; PreDM: prediabetes, SDM; subclinical diabetes.

The cause-effect interaction between a common endocrine disorder and an infectious disease is an important issue to elucidate. Comparison between the stages of glucose abnormalities and disease severity of HCV infection may pave a way to the clarification. HCV core gene transgenic mice study by Shintani et al demonstrated that the ability of insulin to lower the plasma glucose level was impaired without gain in body weight at young age (Shintani et al., 2004). The presence of advanced histological disease in genetically predisposed CHC patients was associated with a higher prevalence of DM and IFG (Zein et al., 2005). There was also a significant linear trend from normoglycemia to T2DM in terms of age, family history of T2DM, and advanced liver fibrosis in CHC patients (Huang et al., 2008). Both experimental and clinical studies provide the evidence that the genuine connection between

HCV infection and T2DM is initiated at early stages of liver disease. HCV infection may contribute to the subtle development of glucose abnormalities at young age.

Characteristics	Anti-HCV (-) Controls	Anti-HCV (+) patients	P value	OR, 95% CI
Patients, <i>n</i>	447	552		
Age (years)	50.5 ± 13.7	52.0±12.4	NS	
Male, <i>n</i> (%)	222 (49.7)	268 (48.6)	NS	
Normoglycemia, <i>n</i> (%)	289 (64.7)	189 (34.2)	<0.001	0.29, 0.22-0.37
Prediabetes, <i>n</i> (%)	145 (32.4)	236 (42.8)	0.001	1.56, 1.20-2.02
Subclinical DM, <i>n</i> (%)	13 (2.9)	127 (23.0)	<0.001	9.98, 5.55-17.9

Table 1. Characteristics of CHC patients without known DM and controls and their glucose abnormalities validated by OGTT. OR: Odds ratio; CI: confidence interval

3.2 Insulin resistance predicts response to peginterferon-alpha/ribavirin combination therapy in chronic hepatitis C patients

Liver has long been regarded as the key player manipulating the homeostasis of glucose metabolism. As a largest reservoir of glucose, the importance of liver in the glucose metabolism draws its much attention from the patients with advanced liver disease. Hepatic diabetes was once recognized when diabetes developed in those who had advanced liver cirrhosis or severe liver injury, on which overt fasting hypoglycemia and/or postprandial hyperglycemia appeared as a common phenomenon. IR is therefore a common feature of some liver diseases, especially with advanced stages. To address the relationship between IR and liver diseases, the extent of liver injury and the impact of liver disease itself on insulin signalling and subsequent glucose metabolic dysregulation should be taken into consideration. Besides skeletal muscle and adipose tissue, liver is the major targets 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.

The measurement of IR in the field of hepatology remains to be investigated in a clinical setting. Although the “gold standard” test for IR assessment is the hyperinsulinemic-euglycemic clamp test. However, the difficulty of techniques and its laborious characteristic much embarrass the wide use of the test. The Homeostatic Model Assessment (HOMA), which has been used in large epidemiological studies, offers an estimate of IR by multiplying the FPG and insulin concentrations and dividing this product by 22.4 or 403 when the glucose concentration is expressed as millimolar or milligrams per deciliter, respectively. A HOMA score close to 1 indicates normal insulin sensitivity, whilst an increase IR circumstance is recognized as the score over 2. 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 races may undermine the accuracy of the measurements (Neuschwander-Tetri, 2008).

HCV may induce IR irrespective of the severity of liver disease and IR may be associated with severe hepatic fibrosis and contribute to fibrotic progression in CHC (Alexander, 2000; Dai et al., 2008; Hui et al., 2003; Petit et al., 2001; Taura et al., 2006). 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 (Hsu et al., 2008).

Combination therapy with PegIFN and ribavirin has been recommended as standard therapy for patients with HCV infection with favorable efficacy (Hui et al., 2003; Petit et al., 2001; Svegliati-Baroni et al., 2007). 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), namely, HCV RNA negativity 24 weeks after treatment, to combination therapy have been elucidated such as the viral factors (e.g. viral G-2 or -3, lower pretreatment viral load) (Hui et al., 2003; Petit et al., 2001; Strader et al., 2004; Svegliati-Baroni et al., 2007; Taura et al., 2006) and host factors (younger age, lower BMI, non-African-American or Asian races and interleukin-28B polymorphisms, etc.) (Fried et al., 2002; Strader et al., 2004; Svegliati-Baroni et al., 2007; Yu et al., 2009; Yu et al., 2011). Glucose abnormalities have also been suggested recently to be a risk factor for nonresponse (Muir et al., 2004). Romero-Gomez et al performed the first study aiming to elucidate impact of IR on the treatment response to PegIFN and ribavirin combination therapy. Achievement of SVR was significantly associated with IR. The SVR rate of G-1 patients with IR (HOMA-IR > 2) was 32.8%, which was significantly lower than that (60.5%) without IR (Romero-Gomez et al., 2005). Dai et al recruited 330 treatment-naïve CHC Taiwanese patients without overt diabetes validated by OGTT. Patients with high HOMA-IR achieved significantly lower rate of SVR than those who with low IR. The significantly lower SVR rate in high HOMA-IR patients than in low HOMA-IR patients was observed in G-1 patients but not in non-G-1 patients (Figure 4). They demonstrated that HCV G-1, pretreatment HCV RNA level and pretreatment HOMA-IR were independent factors associated with SVR. 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 (>400,000IU/mL) (Dai et al., 2009). Conjeevaram et al also showed that IR was independently associated with a lower SVR rate (Conjeevaram et al., 2007). It is noteworthy that the mean HOMA-IR of African and Caucasian American with different levels of steatosis was 3.5 to 6.8, which seemed to be higher than 2.2 of Taiwanese patients. To develop individualized or personalized therapy for CHC, elucidating the changeable predictors of SVR and further manipulating them seems potentially achievable in addition to adjusting the regimens according to the unchangeable viral factors such as HCV genotype. 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. Taken together, these findings suggest pretreatment HOMA-IR is a predictor for the treatment outcomes of combination therapy.

Previous studies have shown that around one to two thirds of liver biopsies from CHC patients have histological evidence of steatosis (Dai et al., 2006; Poustchi et al., 2008; Romero-Gomez et al., 2005). Hepatic steatosis was associated with overweight, hepatic fibrosis and a high TG level. There are also associations between IR, steatosis and liver fibrosis in CHC patient (Conjeevaram et al., 2007; D'Souza et al., 2005; Hsieh et al., 2007;

Powell et al., 2005). Steatosis and fibrosis also predict for treatment response to PegIFN/ribavirin therapy (Heish et al., 2008; Muzzi et al., 2005). Previous study showed IR but not steatosis was independently associated with lower SVR rate (Conjeevaram et al., 2007; Dai et al., 2009; Romero-Gomez et al., 2005). IR has been suggested as the cause, rather than the consequence, of hepatic steatosis and fibrosis in patients with HCV, particularly those with G-1 infection (Sud et al., 2004). The mechanisms for more obvious and important influence of IR than steatosis and fibrosis might need further studies in the future.

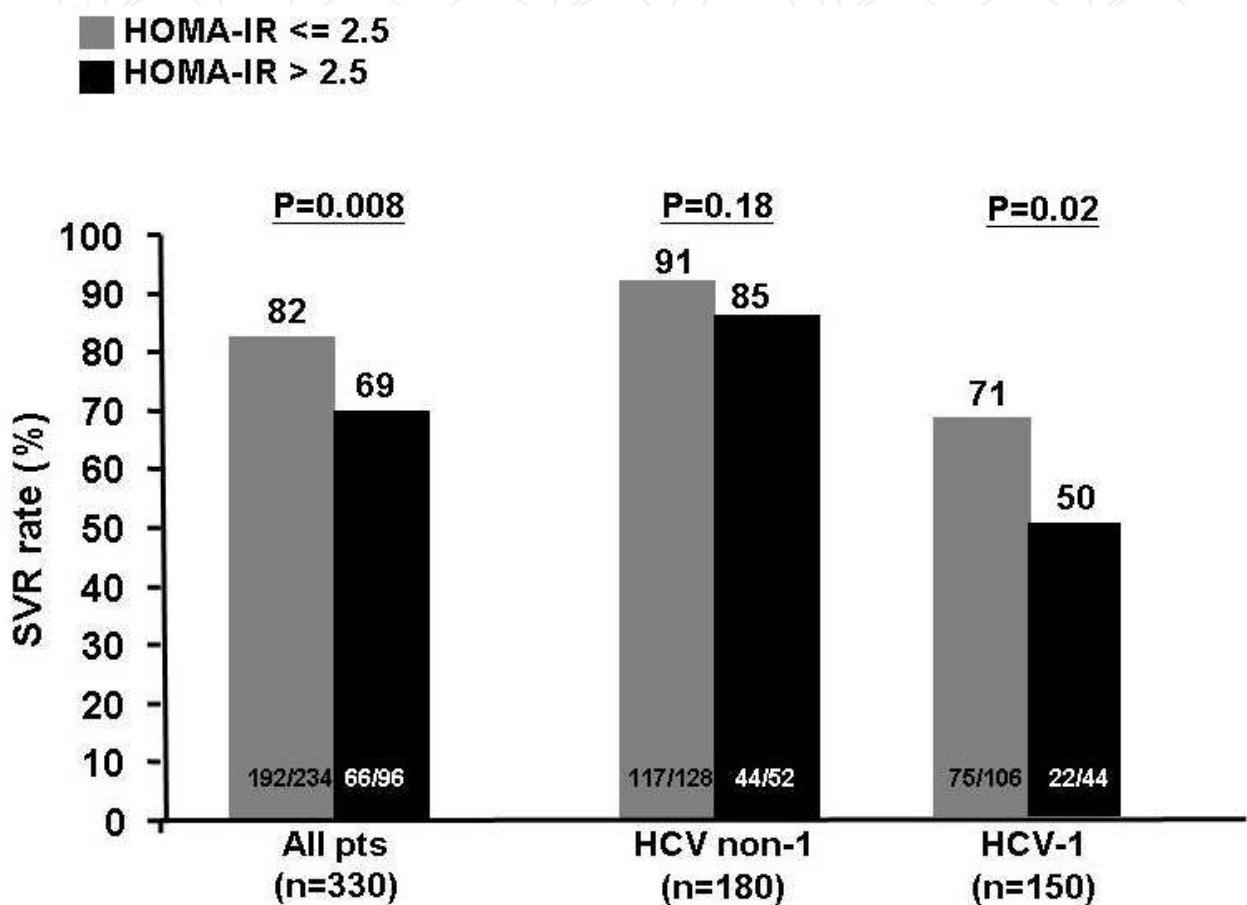


Fig. 4. Sustained virological response rates to combination therapy with pegylated interferon-alpha and ribavirin among chronic hepatitis C patients and stratified by HCV genotype 1b and non-1b infection. The HOMA-IR was defined as high (>2.5 black bars) and low (≤ 2.5 white bars). SVR: sustained virological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

3.3 The impact of pegylated interferon plus ribavirin therapy on insulin resistance and beta-cell function in chronic hepatitis C patients

PegIFN/ribavirin combination therapy is the current standard of care for the treatment of CHC during the past decade (Fried et al., 2002; Hsieh et al., 2007; Yang et al., 2006; Yu et al., 2008). However, IFN is an integral player in immunity and may exacerbate an existing autoimmune tendency, which may subsequently precipitate immune-mediated abnormalities *de novo* (Kawaguchi et al., 2007). Emergences of IR and subsequent DM have been demonstrated with IFN-based therapy, although the mechanism remains to be clarified

(Borg et al., 2007; Chedin et al., 1996). Therefore, the interplay between IFN-based antiviral therapy and alteration of insulin sensitivity deserved to be elucidated. Several studies have suggested an association between viral clearance and/or suppression and relief of IR by IFN-based therapy. Reduced IR and subsequent improved glucose control after IFN therapy had been shown among patients with CHB and CHC infections (Tai et al., 2003). HOMA-IR decreased after treatment in those responders, whilst it remained unchanged in those non-responders. 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 those nonresponders and relapsers (Kawaguchi et al., 2007). Recently, results of the HALT-C study indicated that on-treatment virological suppression correlated with reduction in HOMA-IR at week 24. 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 those responders. The significant decline of HOMA-IR after treatment was observed only in those patients with high pretreatment HOMA-IR, irrespective of SVR achievement (Huang et al., 2011). 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 (Huang et al., 2011). The results suggest a causal relationship between specific genotype and IR. 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 involved in the emergence of IR are multifarious, further long-term follow-up study is needed to elucidate 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. The formulas for the HOMA model of pancreatic beta-cell function are as follows: $\text{HOMA-}\%B = \frac{\text{fasting insulin level } (\mu\text{U/mL}) \times 360}{[\text{FPG (mg/dL)} - 63]}$; the normal value for HOMA- $\%B$ was $>80\%$ (Matthews et al., 1985). Huang et al recruited 277 non-diabetic Taiwanese CHC patients with adequate treatment adherence and showed there was a significance relief of beta-cell function in CHC patients after PegIFN/ribavirin combination therapy, particularly in those responders. Parallel the results that there was no significant decline of HOMA-IR in those responders, the sequential change of beta-cell function might suggest that beta-cell function was recovered earlier than that of IR in CHC patients receiving PegIFN/ribavirin combination therapy (Huang et al., 2011).

4. Related biomarkers

The National Institutes of Health defined biomarker as a “characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” This broad definition includes information that can be derived from characterizing an individual’s genome, transcriptome, proteome, metabolome, markers of subclinical disease, and metabolic end products. Several aspects of effort have been performed dedicating to screen for possible surrogate biomarkers in terms of metabolic manifestations of CHC.

The precise biological mechanisms whereby HCV infection leads to metabolic abnormalities are not fully clear. HCV may induce a Th1 lymphocytes immune-mediated response which leads to activation of tumor necrosis factor (TNF)- α system and elevation of interleukin-6 levels. Meanwhile, HCV directly causes liver steatosis. All the above events may precipitate to 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 (Lecube et al., 2006). HCV-induced inflammatory changes may subsequently lead to increased oxidative stress and increased peroxidation, which evoke systemic inflammatory responses (SIR) than other liver diseases (Lecube et al., 2006b). Therefore, 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 (Figure 5). Meanwhile, SIR may also contribute either directly or indirectly to the disease course, viral response, disease severity, and response to antiviral treatment. Cytokines triggering, which interacts with innate and/or adaptive immune responses, is one of the major concealed players of the scenario.

4.1 Retinol-binding protein 4

For the past decades, several biomarkers have been studied as surrogates of IR. One example is the discovery of retinol-binding protein 4 (RBP4) as a biomarker of IR by DNA microarrays (Tamori et al., 2006; Yang et al., 2005). RBP4, a circulating protein that was highly expressed in the adipose tissue of the adipocyte-specific glucose transporter 4 knockout mice, was demonstrated to be closely related to IR (Yang et al., 2005). IR was induced in mice that were either overexpressing RBP4 or were injected with recombinant RBP4, whereas RBP4 knockout mice showed increased insulin sensitivity. The elevated levels of RBP4 in both adipose tissue and serum were ameliorated when treated with insulin-sensitizer. Reducing serum RBP4 levels ameliorated IR in mice fed a high-fat diet. Graham et al extended this research to humans and showed a correlation between RBP4 levels and the magnitude of IR in subjects with obesity, IGT, or T2DM (Graham et al., 2006). Serum RBP4 levels were even increased in healthy adults with a strong family history of DM. All these interesting findings indicate that RBP4 may serve as a new marker for IR. Lowering RBP4 could be a new strategy for treating T2DM was also deduced then. However, inconsistent observations have been postulated simultaneously and continuously since the discovery of its role in IR (Erikstrup et al., 2006; Janke et al., 2006; Takashima et al., 2006; von Eynatten et al., 2007). Although there was an association between RBP4 and steatosis in G-1 CHC patients, Petta et al suggested RBP4 might be the expression of a virus-linked pathway to steatosis unrelated to IR (Petta et al., 2008).

Liver is the primary source of RBP4 synthesis (80%), the extent of liver injury therefore should be considered when evaluating the correlation of RBP4 with IR (Newcomer and Ong, 2000; Yagmur et al., 2007). Huang et al demonstrated that the increasing change of RBP level from normoglycemia to IGT and T2DM in healthy subjects was indistinct in CHC patients. No correlation of RBP4 levels with HOMA-IR in terms of different stages of glucose tolerance in CHC patients was observed. Intriguingly, in contrast with the parallel increment of IR dependent of histological grading and staging, RBP4 level was inversely correlated with both hepatic necroinflammatory activity and fibrosis stages (Huang et al.,

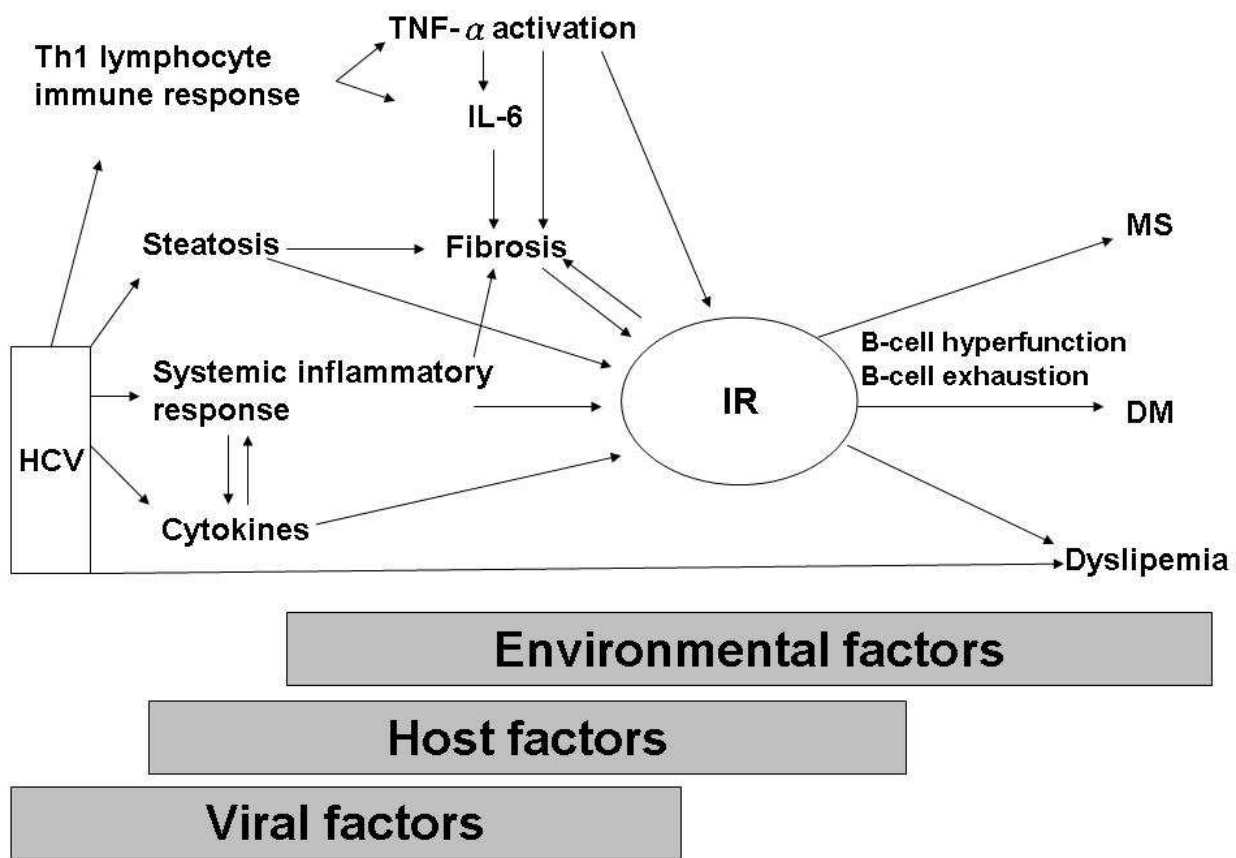


Fig. 5. The possible pathogenic mechanisms leading to the development of insulin resistance and subsequent metabolic disorders. HCV triggers an immune cascades mainly mediated by Th1 lymphocytes. These lymphocytes increase the activation of TNF- α and elevation of interleukin-6 levels. HCV directly leads to steatosis, particularly in those with genotype-3 infection. Meanwhile, 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 diabetes mellitus (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 life, diet, etc) and viral factors (genotype, viral load) is also involved into the complex context. TNF- α : tumor necrosis factor- α ; IL-6: interleukin-6; IR: insulin resistance; MS: metabolic syndrome; DM: diabetes mellitus

2009). Iwasa et al also postulated the similar results in 81 G-1 CHC patients. Moreover, they observed that only patients who had achieved SVR had higher post-treatment RBP4 levels after PegIFN/ribavirin therapy (Iwasa et al., 2009). These clinical studies suggested that the relationship between RBP4 and IR in general population is diminished in CHC patients because of the negative correlation between RBP4 and disease severity. Therefore, it implied that RBP4 may play a limited role in the identification of IR in patients with HCV infection.

4.2 High-sensitivity C-reactive protein

Acute phase reactions with elicited acute phase proteins directly or indirectly from liver are common features in patients with different extent of liver insults ranging from acute liver injury to advanced liver cirrhosis (Ramadori et al., 2001). The features of acute phase proteins include increased C1-inhibitor, C9, C4 and orosomucoid, whilst decreased transferrin and fetuin/a2HS-glycoprotein in CHC patients who responded to IFN-based antiviral therapy (Biro et al., 2000). In the context of cytokines, high-sensitivity C-reactive protein (hs-CRP) has been shown to be closely related to the occurrence of SIR (Koenig et al., 2008). It plays as a major role in the scenario of various chronic liver diseases, such as non-alcoholic fatty liver disease and nonalcoholic steatohepatitis (Kogiso et al., 2009; Riquelme et al., 2009). Serum hs-CRP levels were elevated in patients with IR and were correlated with MS (Ridker et al., 2003; Yudkin et al., 1999). Moreover, hs-CRP has been shown to predict future risks for cardiovascular disease and related mortality (Zacho et al., 2008; Zethelius et al., 2008). With respect to hepatological views, hs-CRP is a liver specific acute-phase protein, and its expression in hepatocytes is closely related with proinflammatory cytokines such as TNF-alpha, interleukin-1 and interleukin-6 (Kushner, 1982). The relationships between HCV infection and vascular atherosclerosis remain an argument of debate (Ishizaka et al., 2002; Moritani et al., 2005; Oyake et al., 2008). There were discrepant results of the association of hs-CRP level and anti-HCV seropositivity in different study groups (Floris-Moore et al., 2007; Kalabay et al., 2004; Nascimento et al., 2005; Reingold et al., 2008; Tsui et al., 2009; Yelken et al., 2009). Recent studies demonstrated CHC patients had a higher serum hs-CRP level (> 3 mg/L, a condition indicative of a high cardiovascular risk) than healthy controls (Zacho et al., 2008). CHC patients with elevated hs-CRP had substantially higher levels of lipid profiles. However, advanced liver diseases may be associated with decreasing cholesterol level and the extent of liver injury should be taken into account when addressing this issue. Moreover, the lipid profiles are reflected by multiple factors such as race, age, gender, life style and meal habits. Therefore, it might be too conclusive to imply that lipid profiles were the major factors correlated with hs-CRP level in CHC patients. Nevertheless, the observation suggested that hs-CRP may be used as a complementary surrogate marker for cardiovascular risks in CHC patients. Further study addressing the sequential changes and the correlation between lipid profiles and hs-CRP in a long-term follow-up basis will be needed to elucidate this intriguing issue.

Hs-CRP level was significantly decreased after PegIFN/ribavirin combination therapy, particularly for those with viral suppression. It may suggest that SIR in HCV infection could effectively be relieved after antiviral therapy, particularly in patients achieving an SVR. Intriguingly, among those non-SVR patients, decreases of serum hs-CRP levels were significantly observed only in relapsers but not in non-responders. It has been shown that those relapsers have more favorable outcomes after re-treatment programs compared with non-responders (Keeffe, 2005). The decreased SIR in relapsers, which was reflected by significantly decreased hs-CRP level, may in a part contribute to the favorable outcomes. It is noteworthy whether the non-responders carry a higher risk of developing cardiovascular events and it awaits further intervention.

4.3 PI3K/Akt

The precise mechanisms whereby SIR triggered by HCV infection is not fully clear. Disarrangement and/or dysregulation of intracellular signal trafficking subsequent to

interaction with HCV characteristic proteins have been postulated to be a major pathogenic mechanism of the inflammatory changes (Bowen et al., 2005). One example of such research is Akt. It is a 57 kDa serine/threonine protein kinase B (PKB) expressed in fibroblasts, adipocytes and skeletal muscle, mediates many of the downstream events of phosphoinositide 3-kinase (PI3K) signaling. It is a critical intracellular signal activated by insulin and other growth factors and is also essential for most of the metabolic effects of insulin (Farese et al., 2005). Upon binding of insulin to its cell surface receptor, activation of its tyrosine kinase activity results in the phosphorylation of multiple substrates involved in its downstream effector functions. Activation of PI3K and phosphoinositide-dependent protein kinase signalling pathway results in the activation of multiple other related molecules, mediates intracellular signals to regulate a variety of cellular responses, including anti-apoptosis, proliferation, cell cycling, protein synthesis, glucose metabolism, and telomere activity (Noguchi et al., 2008). Experimental studies demonstrated that HCV proteins can activate PI3K/Akt pathway and expression of HCV core protein increased hepatic stellate cell (HSC) proliferation in a PI3K/Akt dependent fashion (Bataller et al., 2004). The increased phosphorylation correlated with increased IR to a variety of apoptotic stimuli (Banerjee et al., 2008; Street et al., 2005). PI3K/Akt signaling pathway was a concealed player involving in inflammatory process, thus contributed to HSC activation, liver fibrosis progression, and apoptosis (Aleffi et al., 2005). Inhibition of PI3K signaling in HSC, which in turn reduced Akt activation, blocked the progression of liver fibrosis (Son et al., 2009). In addition, activation of the Akt signalling pathway has been demonstrated to contribute to hepatocarcinogenesis and predict outcomes of HCC in patients with HCV infection (Schmitz et al., 2008). Hepatic Akt expression of immunostaining was also significantly associated advanced fibrosis, a higher necroinflammatory activity, a lower BMI, a lower LDL-C and a lower gamma glutamyl transferase levels (Huang et al., 2011).

Since HCV-induced liver fibrosis has been demonstrated to be reversible after successful eradication of HCV infection, a long-term follow-up study with regard to the sequential change of Akt expression in patients receiving antiviral therapy is needed to elucidate this issue. In addition, activation of the Akt signalling pathway has been demonstrated to contribute to hepatocarcinogenesis in patients with HCV infection. Further follow-up study with respect to the correlation between Akt expression and liver cancer development also deserves.

4.4 Visfatin

Adipose tissue has emerged as a major endocrine organ. These adipokines play major roles in key aspects of metabolism, such as energy intake and expenditure, IR, fatty acid oxidation, inflammation, and immunity. Visfatin, as a visceral fat-specific adipokine, is a 52 kD protein that has been cloned already years ago as pre-B cell colony-enhancing factor (PBEF). Recently, visfatin was found to exert insulin-mimicking effects and may activate the intracellular signaling cascades for insulin (Fukuhara et al., 2005). Increasing visfatin level was significantly associated with T2DM (Chen et al., 2006; Dogru et al., 2007). Serum visfatin level was higher in obese than non-obese patients, and it was lower in non-alcoholic steatohepatitis patients than in those with simple steatosis or obese controls (Jarrar et al., 2008). In addition, visfatin level was shown to predict the presence of portal inflammation in non-alcoholic fatty liver disease patients (Aller et al., 2009). Visfatin was preferentially

expressed by visceral adipose tissue compared with subcutaneous fat (Fukuhara et al., 2005). A positive correlation between visfatin and BMI as well as visceral fat mass has been reported (Hammarstedt et al., 2006). However, during the past years, contradictory results regarding waist circumference, glucose level, IR, visceral and subcutaneous adipose tissues have also been emerged in a clinical setting (Sommer et al., 2008). Berndt et al demonstrated that serum visfatin level did not correlate with visceral fat mass and that mRNA expression of the gene encoding visfatin was similar in visceral and subcutaneous adipose tissue (Berndt et al., 2005). Pagano et al demonstrated that serum visfatin level was decreased by approximately 50% in obese patients compared with controls. Furthermore, a negative correlation was found between serum visfatin level and BMI (Pagano et al., 2006). In the aspect of HCV infection, CHC patients tended to have a higher visfatin level than that of healthy controls. Serum visfatin level was correlated significantly with histological activity index scores and fibrosis stages, namely, disease severity in CHC patients (Huang et al., 2011). It hence implied that visfatin could be a potential biomarker for prediction of disease severity in HCV infection. The concordant results in different entities of liver diseases provided evidence for previous experimental studies indicating that visfatin was involved into inflammatory process network (Lim et al., 2008). On the other side, the studies addressing the correlation between visfatin and HCV genotypes were not concordant (Kukla et al., 2010). There was no significant correlation between visfatin and viral load, and treatment response to PegIFN/ribavirin therapy. Further study is warranted to clarify in which a concealed player or a bystander of the necroinflammatory and fibrogenetic scenarios visfatin behaves.

There was a tendency for higher visfatin levels in CHC patients with lower BMI (Huang et al., 2011; Kukla et al., 2010). MS was also negatively correlated with visfatin level in CHC patients. In addition, the extent of glucose abnormalities was not significantly correlated with visfatin level. These observations may imply that visfatin was not related to IR (Pagano et al., 2006). Kukla et al postulated that visfatin may play a dual role as a pro-inflammatory and/or protective factor (Kukla et al., 2010). Taken together, the speculations regarding the role of visfatin in CHC patients include 1) visfatin may not be one of the initiators in the context of metabolic derangements; 2) visfatin may not be involved into the link between obesity and IR in a clinical setting, at least among CHC patients. Therefore, its precise endocrine role deserved to be further clarified in HCV infection.

Several cytokines, particularly adipokines, have been investigated in terms of the link between HCV infection, steatosis, fibrosis, and metabolic abnormalities. These include leptin, adiponectin, apelin, resistin, TNF- α , interleukins, etc (Liu et al., 2005; Marra et al., 2009). It is informative and helpful for the elucidation of pathogenic mechanisms to assess the interaction between related biomarkers and clinical profiles of HCV infection, such as metabolic, virological, and histological factors.

5. Conclusion

Metabolic disorders are characteristic in patients with HCV infection. Besides established liver injury, the multiple extrahepatic metabolic disorders lead to a certain extent of impact on the disease activity, disease course, clinical outcomes, and treatment efficacy of current therapy. Enormous challenges for patient management have been arisen in parallel with the

occurrence of these metabolic disorders. Although the precise mechanisms contributing to each aspect of metabolic abnormalities are not fully clarified, inspiring data and studies during the past decades have much enhanced our knowledge of this unique link between a viral hepatitis disease and many common metabolic manifestations. With the rapid progression of new therapy for CHC, i.e. direct acting antivirals, in the past few years, the interaction between HCV infection and metabolic disorders will become clearer. Meanwhile, recent promising data based on genome-wide association studies largely explore our understanding of the impact of host susceptibility on the treatment efficacy of CHC. It may also pave the way for the future study regarding the genetic and/or proteomic aspects of metabolic abnormalities in HCV infection. On the other side, management of the metabolic disorders mainly depends on both pharmaceutical intervention and lifestyle modifications, such as exercise, diet control and weight reduction for T2DM and dyslipemia. Whether these interventions play a role in the disease course and prognosis of CHC patients deserves to be elucidated in the future.

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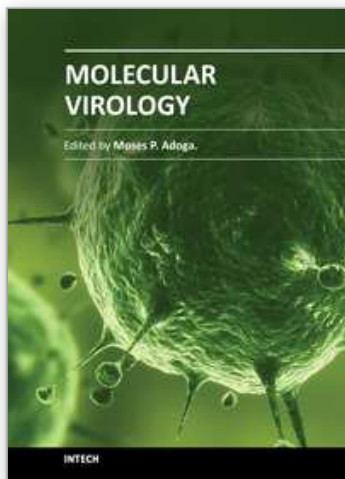
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This book covers various aspects of Molecular Virology. The first chapter discusses HIV-1 reservoirs and latency and how these twin phenomena have remained a challenge to eradication. Aspects regarding the molecular evolution of hepatitis viruses including their genetic diversities with implications for vaccine development are treated in the second chapter. Metabolic disorders that are a consequence of hepatitis C virus infection are discussed in the succeeding chapter. The following two chapters discuss influenza C virus and the applications of viral vectors in therapeutic research. Avian influenza is handled in the sixth chapter and the therapeutic potential of belladonna-200 against japanese encephalitis virus infection is discussed in the succeeding chapter. The last two chapters discuss baculoviruses and their interaction with polydnviruses. Researchers, lecturers and students will find this book an indispensable companion.

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