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• *REVIEW* •

Chronic hepatitis C virus infection and post-liver transplantation diabetes mellitus

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Abstract

Patients with chronic hepatitis C virus (HCV) infection have a significantly increased prevalence of type 2 diabetes mellitus compared to controls or HBV-infected patients. Moreover, the incidence rate of post-liver transplantation diabetes mellitus (PTDM) also appears to be higher among patients with HCV infection. PTDM is often associated with direct viral infection, autoimmune disorders, and immunosuppressive regimen. Activation of tumor necrosis factor-α may be the link between HCV infection and diabetes. In this article, we reviewed the epidemiologic association between HCV infection and PTDM, highlighting the most recent pathophysiologic insights into the mechanisms underlying this association.

Key words: Hepatitis C virus; Post-liver transplantation diabetes mellitus; Tumor necrosis factor; Immunosuppressive therapy

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INTRODUCTION

The last two decades have seen an increase in various types of organ transplantation for the treatment of end stage organ diseases. Prevention of organ rejection requires long-term immunosuppressive therapy, which places recipients at the increasing risk of infection and metabolic disorders, such as recurrent hepatitis C virus (HCV) infection and post-liver transplantation diabetes mellitus (PTDM). Recipients with HCV infection have a higher incidence of PTDM, which depends on the degree and duration of immunosuppressant[1]. On the other hand, the occurrence of PTDM is associated with direct viral infection, autoimmune disorders[3], and immunosuppressive regimen, notably tacrolimus[4]. PTDM characteristically shows insidious onset and aggressive behavior thereafter. PTDM in HCV-infected patients might be partially or completely recovered after reduction or switching of immunosuppressive therapy[5].

PTDM AND HCV ASSOCIATION: RISK FACTORS

The high prevalence of diabetes mellitus, especially type 2 diabetes mellitus (type 2 DM) in HCV-infected patients comes from epidemiologic studies (Table 1), most of which are case control studies,[6,7,9,10-12,14] in addition to two multicenters and cohort[8,13]. Risk factors resulting in the increasing prevalence of type 2 DM in HCV-infected patients include positive family history of diabetes and black ethnicity[15]. Thus, it is conceivable that HCV leads to type 2 DM in susceptible hosts. Immunogenetic studies suggest that an infectious process coexists in patients with type 2 DM and chronic liver disease and HLA-DR2, -DR51, -DQB6 haplotypes provide a two- and three-fold relative risk for the development of diabetes[16].

It is reported that liver transplantation recipients with HCV infection have a four- to eight-fold prevalence of diabetes compared with recipients with other viral or cholestatic liver diseases 1 year after liver transplantation. A recent study of 260 HCV-infected patients has confirmed that insulin resistance is an independent predictor of the degree of fibrosis, and that insulin sensitivity has a significant correlation with serum aspartate aminotransferase, histological activity index and degree of fibrosis[18] in non-diabetic HCV-infected patients. Gray *et al*.[17], observed that abnormal liver function tests are found in 72.3% of HCV-positive diabetic patients and in only 24.7% of HCV-negative diabetic patients ($P<0.001$). In summary, the occurrence of PTDM seems to be associated with HCV infection.

PATHOPHYSIOLOGY

The pathophysiologic mechanism underlying the development of PTDM in patients with HCV infection has not been clearly illustrated. Possible mechanisms are shown in Figure 1.

Tumor necrosis factor-alpha (TNF-α)

A study of liver biopsy specimens from non-diabetic HCV-infected patients has revealed significant impairments in the insulin-signaling pathway[19], which is strikingly similar to the known effect of tumor necrosis factor-α (TNF-α) on insulin resistance[20]. The role of TNF-α in the pathogenesis of this HCV-associated insulin resistance state is strongly

Table 1 Studies of PTDM in patients with chronic HCV infection

PTDM (%)		RR (95%CI)	Study description	Reference
HCV+	HCV-			
33	12	3 (0.98-9.6)[b]	Case control	Zein *et al.*, 2000
34	9.8	0.95 (0.2-3.9)[a]	Case control	Bigam *et al.*, 2000
20.9	-	1.9 (0.4-14.2)	Multicenter	Khalili *et al.*, 2004
43	13	1.9 (1-2.6)[b]	Case control	AlDosary *et al.*, 2002
64	28	2 (0.9-4.6)[b]	Case control	Baid *et al.*, 2002
29	10	2 (0.96-4.3)[b]	Case control	Bigam *et al.*, 2000
72	37	4.8 (0.8-30)[d]	Case control	Yildiz *et al.*, 2002
62	8	11.6 (1.7-79)[b]	Cohort	Delgado-Borrego *et al.*, 2004
18.29	-	-	Case control	Parolin *et al.*, 2004

[a]$P<0.05$, [b]$P<0.01$, [d]$P<0.001$ *vs* control.

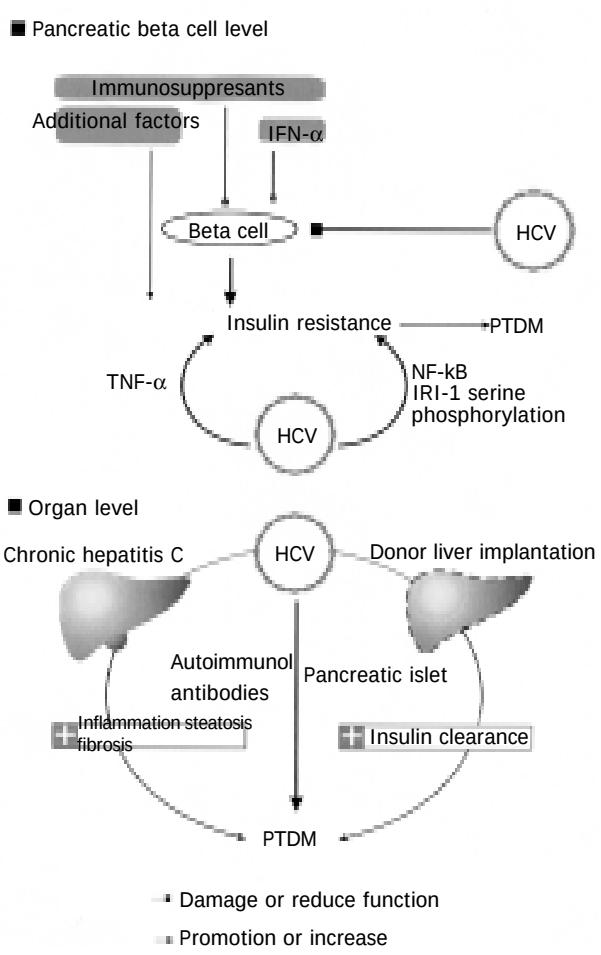

Figure 1 Possible mechanism underlying the development of PTDM in HCV infection (at least four mechanisms contribute to exacerbation of insulin resistance). (1) Chronic activation of TNF-α, which plays a key role not only in the production of and response to HCV itself, but also in the development of insulin resistance. Additional factors for developing PTDM in HCV-infected patients, including obesity, black ethnicity, and aging, are known to be associated with increased TNF-α independent mechanisms; (2) the increased clearance of insulin that occurs in post-transplant recipients thus creates a reactive hyperinsulinemic medium, and that in turn might enhance insulin resistance; (3) a bi-directional relationship between liver disease and diabetes is possible, as both insulin resistance and PTDM can adversely affect HCV liver disease; (4) directly diabetogenic effect of immunosuppressive therapy on pancreatic β cell.

supported by findings of elevated intra-hepatic TNF-α and amelioration of the metabolic abnormalities after TNF-α antibodies are administered[2]. The interrelationship between HCV and other predisposing conditions of PTDM could partly be mediated by TNF-α and most of the established risk factors for PTDM, such as obesity, aging[21], black ethnicity[22], and a family history of type 2 DM[23].

HCV per se

HCV replicates in hepatocytes, but its genome has been identified in a number of other tissues, including pancreatic acinar cells and epithelial cells of the pancreatic duct[24]. The destruction of pancreatic β cells could be mediated either directly by HCV or by HCV-induced immune responses, but evidence is scanty[3]. More recently, a transgenic mouse model that specifically expresses the HCV core protein in hepatocytes has been studied[2]. These animals had insulin resistance at an early age, and when challenged by a high fat diet, they developed glucose intolerance. Further characterization of the metabolic defects in these animals revealed that insulin resistance was caused mainly by failure of insulin to suppress hepatic glucose production. Piquer *et al.*[25], assessed the prevalence of islet cell autoantibodies in 303 non-selected HCV-infected patients (277 non-diabetic and 26 type 2 DM patients) and 273 sex- and age-matched control subjects, and found that patients with HCV have no significantly higher pancreatic autoantibodies compared with controls. However, it was reported that type 1 DM occurs more frequently in HCV patients treated with interferon (IFN) as a result of amplification of previously existing autoimmunity against pancreatic β cells, and that treatment of healthy volunteers with IFN can stimulate counter-regulatory hormone secretion, impair glucose tolerance and insulin sensitivity and induce insulin clearance, suggesting that HCV-induced immune response might be involved in the development of insulin resistance[26].

Immunosuppressive therapy

The overall effects of immunosuppression may potentiate the diabetogenic effects of HCV infection by enhancing the level of viral replication. A study on the effects of corticosteroids on post-transplant levels of viremia and PTDM showed that pulsed intravenous methylprednisolone therapy is associated with transient 4- to 100-fold rise in HCV RNA levels and the reduced translocation of glucose transporter 4 from cytosol into membrane, and that higher HCV RNA level is correlated with increased severity of graft and islet injury[30,45,46]. Immunosuppressive agents, especially steroids and calcineurin

inhibitors, are diabetogenic. The direct and indirect effects of corticosteroids, CyA on pancreatic β cells are well documented. With regard to FK506, the available data are not as extensive as for CyA, and its role in low blood insulin levels *vs* insulin resistance has not been fully evaluated. Human pancreatic allograft biopsies demonstrating both FK506 and CyA can induce structural damage of the graft islets, for example, cytoplasmic swelling, vacuolization, apoptosis, and abnormal immunostaining for insulin and the absent or reduced dense core secretory granules in the β cells. These changes are related to the doses of FK506 and/or CyA used. Although CyA and FK506 bind to different target molecules, both drugs inhibit or perturb the intermediate molecular events of insulin signal transduction (serine phosphorylations/dephosphorylations) in the same fashion. As a result, insulin signal fails to dephosphorylate the cytoplasmic component of the nuclear factor of activated signal transduction and transcription of insulin-sensitive gene, thus incorporating insulin resistance[27,28].

Organ level

Nonalcoholic fatty liver disease is associated with type 2 DM and the metabolic syndrome in patients with HCV[29]. However, the role of HCV as a risk factor for fatty liver has been questioned. It was reported that obesity and hyperlipidemia have a confounding effect on the association between HCV and steatosis[30]. In one study, serum ferritin levels were determined in 123 HCV-infected patients (55 diabetic and 68 non-diabetic patients)[32]. Increased iron store, which occurs in up to 40% of patients with chronic HCV infection[31], has been linked to the pathogenesis of diabetes development in those patients. The hepatic parasympathetic nerves are mediated by the activation of the Ach/NO/cGMP pathway involved in the secretion of a hepatic insulin sensitizing substance to mediate peripheral insulin sensitivity[41,42]. Schneiter *et al.*[33], found that liver transplantation recipients have severe insulinopenia as a result of the increased insulin clearance[33].

CLINICAL FEATURES

PTDM shares many similarities with type 2 DM in that the onset can be insidious, and individuals may experience glucose intolerance and may be asymptomatic for years[5]. The development of PTDM involves two distinct phases: (a) patients are initially at the greatest risk during the first 6 mo post-transplantation, and (b) the number of patients developing diabetes increases progressively thereafter. This has been illustrated by a study of 618 liver allograft recipients in which 7.2% of patients developed diabetes in the first 6 mo after transplantation, but then the percentage of cases increased linearly, leading to cumulative percentages of 7.1%, 10.4%, 13.2%, 20.5%, and 29.8%, respectively after 1, 3, 5, 10, and 15 years[34]. In a recent study, unadjusted cumulative incidences of diabetes 3, 12, and 36 mo after kidney transplantation were 15.6%, 25.6%, and 35.4% compared to 8.8%, 15.4%, and 23.4% in patients who were HCV negative at transplantation ($P<0.0001$)[35]. The potentially asymptomatic and/or transient nature of diabetes after transplantation makes the condition difficult to diagnose, thus underlining the importance of establishing a precise definition. It is recommended that the definition and diagnosis of PTDM should be based on the currently accepted definition of diabetes mellitus by the American Diabetes Association[5]. Diabetes mellitus is diagnosed by three fasting glucose measurements in the plasma above 7.0 mmol/L and/or antidiabetic medication (oral antidiabetic drugs or insulin), excluding periods requiring total parenteral nutrition or high steroid dosages for treatment of acute rejection, which may transiently impair glucose tolerance. After liver transplantation, patients with diabetes mellitus are classified either as non-insulin-requiring PTDM when taking only oral antidiabetic drugs or diet or as insulin-requiring PTDM when they require insulin injections. This classification of the patients should be done more than 1 year after liver transplantation[36]. Some preliminary reports suggest that pre-emptive therapy with IFN or a combination of IFN plus ribavirin may lead to less severe HCV infection recurrence after liver transplantation[43,44]. However, there are no controlled studies evaluating the prophylaxis of IFN in PTDM with HCV infection.

IMPLICATIONS

The HCV-diabetes association represents a major public health problem. Hundreds and thousands of patients in the USA alone are probably affected, and many more may have impaired glucose tolerance. Diabetes-related micro- and macrovascular complications are likely to occur, and the ongoing hepatic inflammatory response may contribute to atherogenesis. Furthermore, a putative bi-directional relationship between HCV-induced liver disease and diabetes may occur. Both insulin resistance and diabetes can adversely affect the course of chronic hepatitis C, and lead to enhanced steatosis, steatohepatitis, and liver fibrosis[37,38]. Moreover, recent evidence strongly suggests that steatosis and diabetes may also significantly enhance the risk of hepatocellular cancer[39,40].

FUTURE DIRECTIONS

There is evidence that HCV infection is related with the presence of PTDM. However, several questions remain to be answered. Firstly, randomized trials aimed to evaluate interactions of immunosuppressive regimens for the prophylaxis and treatment of PTDM are scarce. Secondly, the antiviral therapy for intervention remains to be determined. Finally, information is needed to clarify and diminish the effect of PTDM on quality of life and long-term outcomes. Further studies are necessary to evaluate the prognostic meaning of PTDM and the predictive factors for PTDM and to elucidate the pathophysiologic mechanisms.

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