EDITORIAL COMMENT

Chronic Hepatitis C and Diabetes Mellitus

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Introduction

Hepatitis C virus (HCV) affects approximately 170 million people worldwide. More than 80% of patients with HCV infection progress into chronicity, 20–30% of patients with chronic hepatitis C progress to cirrhosis after 10–20 years of follow-up, and some develop hepatocellular carcinoma.[1] Chronic HCV infection is the most important cause of liver transplantation in Western countries. Extrahepatic manifestations in patients with chronic hepatitis C have been clinically noticed. Among them, cryoglobinemia, membranoproliferative glomerulonephritis, and porphyria cutanea tarda are definitely associated with HCV infection.[2] For the remaining manifestations, such as lichen planus, autoimmune thyroiditis, Sjögren's syndrome, and low-grade B-cell lymphoma, however, the role of HCV is still under debate. Recently, the association of chronic hepatitis C with diabetes mellitus (DM) has gained much attention.

A large number of clues have suggested the potential role of a common hepatotrophic virus in developing diabetes. As many as 80% of patients with cirrhosis show glucose intolerance, and 10–20% of them have DM.[3] Physiologic glucose homeostasis is maintained by a dynamic equilibrium between endogenous glucose production and glucose use. These processes are regulated mainly by insulin and glucagons. However, liver also plays a crucial role in both endogenous glucose production and glucose use.[4] Glucose intolerance has been demonstrated in cirrhotic patients because of insulin resistance caused by a postreceptor defect, decreased binding of insulin to target tissue, and inadequate response of the beta cells of the pancreas to appropriately secrete insulin to overcome the defect in insulin action.[5]

Epidemiologic Studies of Serum HCV Antibodies (Anti-HCV) in Patients With Type 2 DM

Increased prevalence of positive serum anti-HCV has been found in patients with DM.[6,7] Simo et al[7] showed a significantly higher prevalence rate of positive serum anti-HCV (11.5%) in 176 diabetic patients when compared with 2.5% in 6,172 blood donors. In this issue, Chen et al[8] evaluated serum anti-HCV and hepatitis B surface antigen (HBsAg) among 820 type 2 DM patients and 905 non-DM healthy check-up subjects. They reported a higher seroprevalence of HCV infection among patients with type 2 DM (6.8%) than in the control group (2.6%) (odds ratio: 2.87; 95% confidence interval: 1.51–5.46), but no difference in positive HBsAg between the groups (13.5% vs 12.4%). They found a 2.8 times higher risk of hepatitis C in Chinese patients with type 2 DM.[8] Chen et al's results are consistent with previous reports indicating the possible association between type 2 DM and chronic hepatitis C. However, the risk factors of HCV infection should be evaluated in detail in this kind of study. History of blood transfusion, tattooing, intravenous drug abuse, hemodialysis, abortion, nondisposable needle exposure, and frequent dental procedures are all common routes for contracting HCV infection in this area.[9] High prevalence of chronic hepatitis B in Taiwan is mainly due to perinatal infection through an HBsAg-positive mother or horizontal transmission at preschool age. Thus, the similar HBsAg prevalence rate between type 2 DM and controls could not exclude the risk of nondisposable needle injection in contracting adult HCV infection.

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Epidemiologic Studies of DM in HCV-related Diseases

In 1994, Allison et al[10] first reported the association of chronic hepatitis C with DM, and gained extensive attention thereafter. A number of studies have shown that 13–33% (median 25%) of patients with chronic HCV infection are diabetic.[11–13] This prevalence is significantly higher than that in matched healthy controls. In 2000, Mehta et al[14] reported an important survey addressing a link between DM and HCV status in a representative sample of the general population of the USA through the Third National Health and Nutrition Examination Survey (NHANES III). After adjustment for DM confounding factors such as age, race, high body mass index, and low socioeconomic status, they found that persons older than 40 years of age with HCV infection were 3 times more likely than those without HCV to have type 2 DM (odds ratio: 3.77; 95% confidence interval: 1.8–7.87).

Additionally, a higher prevalence of DM has been reported in HCV-infected patients compared with those with other liver diseases such as chronic hepatitis B, primary biliary cirrhosis, and primary sclerosing cholangitis.[11–13] The post-liver transplant setting also provides a unique opportunity to address the relationship between HCV and DM. The prevalence of DM is higher in HCV-positive than in HCV-negative liver transplant recipients.[15] In addition, *de novo* transient or persistent DM has occurred more frequently in HCV-infected transplant recipients than in HCV-negative subjects.[16] Antonelli et al[17] also reported a large excess of type 2 DM (12.6%) among noncirrhotic chronic hepatitis C patients over a sample of the general population or age-matched noncirrhotic chronic hepatitis B patients, indicating that the associations between chronic HCV infection and DM are independent of cirrhosis. All of these studies disclosed a close relationship between HCV infection and the development of DM.

Risk Factors of HCV Infection in the Development of Type 2 DM/Impaired Fasting Glucose

Despite the close relationship between HCV infection and DM, the actual pathogenesis for HCV infection to develop type 2 DM remains to be established. Type 2 DM is a complex, multisystem disease with a pathophysiology that includes a defect in insulin secretion, increased hepatic glucose production, and resistance to the action of insulin, all of which contribute to the development of overt hyperglycemia. In addition, obesity, aging, and genetic factors such as family history of DM all may contribute to the development of type 2 DM. All these factors make it difficult to evaluate the pathogenic role of HCV infection in the development of type 2 DM. In our previous study, an age > 57 years, family history of DM, body mass index > 25 kg/m^2, and previous interferon treatment were all independent factors for the development of type 2 DM in patients with chronic hepatitis C.[18] Interferon has been shown to induce insulin resistance in the splanchnic and peripheral tissues of patients with HCV.[19] Zein et al[20] found that, after excluding chronic hepatitis C patients who received previous interferon treatment, higher fibrotic stages in liver histology and family history of DM were closely associated with higher prevalence of DM and impaired fasting glucose in patients with chronic hepatitis C.

Possible Pathogenesis of HCV Infection in the Development of Type 2 DM

The pathogenic mechanisms causing DM in patients with HCV infection are still not well understood, although both insulin resistance and impaired insulin secretion have been considered to play an important role in the development of DM. In a transgenic mouse model, the reduction of plasma glucose concentration after intraperitoneal insulin injection was impaired in HCV core-gene transgenic mice, displaying a higher plasma glucose level than in control mice, as well as significantly higher basal serum insulin levels, indicating insulin resistance in HCV core-gene transgenic mice.[21] Several studies have demonstrated insulin resistance in patients with HCV-related chronic hepatitis, using a homeostasis model assessment (HOMA).[22] Narita et al[23] demonstrated that, using HOMA methods, both insulin resistance and beta-cell dysfunction contributed to glucose intolerance in chronic hepatitis C patients. Delgado-Borrego et al[24] reported that HCV is independently associated with increased insulin resistance among orthotopic liver transplant recipients. Petit et al[25] demonstrated that insulin resistance in nondiabetic HCV-infected patients is correlated with the staging of liver fibrosis and may occur early in the course of HCV infection, even in nondiabetic patients.

More recently, the role of tumor necrosis factor (TNF)-α in the pathogenesis of DM in chronic hepatitis C patients has gained extensive interest.[26] TNF-α has been shown to inhibit insulin-stimulated tyrosine phosphorylation of insulin receptor and insulin receptor substrate 1 in adipocytes, stimulate lipolysis, and increase

serum-free fatty acids, leading to insulin resistance in muscle and liver, mediate hepatic insulin resistance to increase hepatic glucose production, and down-regulate genes in adipocytes encoding proteins such as insulin receptor substrate 1, glucose transporter-4, peroxisome proliferator-activated receptors, and adiponectin. In addition, TNF-α may reduce beta-cell function by direct toxic effects, further contributing to the development of DM. Recent studies have shown significantly higher levels of soluble TNF-α receptors in diabetic HCV patients than in nondiabetic HCV patients and controls.[27] A link between chronic HCV infection, TNF-α, and type 2 DM is an attractive hypothesis.

The HCV–diabetes association represents a major public health problem. Between 2% and 5% of the urban population in Taiwan are positive for serum anti-HCV, and highly HCV-endemic villages were noted in the west coast and central part of Taiwan.[1] Many of them may have impaired glucose tolerance or DM. Diabetes-related microvascular and macrovascular complications are likely, and the ongoing hepatic inflammatory response may contribute to atherogenesis. Furthermore, both insulin resistance and diabetes can adversely affect the course of chronic hepatitis C and lead to enhanced steatosis, steatohepatitis, and liver fibrosis,[28] which may increase the risk of cirrhosis and hepatocellular carcinoma. Further studies concerning these issues are ongoing.

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