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EDITORIAL

An Intriguing Relationship between Type 2 Diabetes Mellitus and Hepatitis C Virus Infection: The Renal Perspective

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Type 2 diabetes mellitus has emerged as the commonest cause of end-stage renal disease (ESRD) over the past three decades. It accounts for 30% to 50% of patients on renal replacement therapy (RRT); nearly 80% of patients are managed with hospital-based hemodialysis. Chronic hepatitis C virus (HCV) infection is endemic among patients on RRT, especially among those undergoing maintenance hemodialysis (HD) [1, 2]. Therefore, both the disorders are prevalent and coexist among patients with ESRD and frequently cause complications in a considerable majority of the affected patients resulting in poor outcomes.

A number of studies have demonstrated a higher prevalence of type 2 diabetes mellitus in patients with HCV in comparison to general population [2-6]. Mehta *et al.*, in a recent epidemiological study based on data from the Third National Health and Nutrition Examination Survey (NHANES III), provided compelling data for the distinctive association between chronic HCV infection and type 2 diabetes mellitus [3]. In this report, anti-HCV positive subjects (>40 years old) had a significantly higher prevalence (OR=3.77) of type 2 diabetes mellitus compared with HCV-negative subjects. Likewise, Egyptian investigators observed a two-fold higher incidence of type 2 diabetes mellitus in patients who had HCV infection compared with those who did not [4].

Although precise mechanisms involved in the development of glucose intolerance are not well understood, it seems that the virus itself, through its core protein can modify the metabolic profile of HCV-infected patients which leads to development of type 2 diabetes mellitus. Mechanistic studies have revealed that HCV encoded proteins may cause post-receptor defects in insulin receptor substrate 1 (IRS-1). It may also associate with the insulin receptor (IR) and insulin signaling defects in hepatic IRS-1 tyrosine phosphorylation and phosphatidylinositol 3-kinase (PI3k) activation that may contribute to development of insulin resistance and subsequent development of type 2 diabetes mellitus in patients with HCV infection [7] (Fig. 1).

On the other hand, there is comparatively little data relating to the vulnerability of type 2- diabetics to the acquisition of HCV infection [6-10]. Data from the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study, USA, imply three times higher predisposition of adult diabetic patients to infection-related mortality as compared to the non-diabetic population [8]. Earlier Ozyilkan *et al.,* [10] and recently Sangiorgio *et al.,* [11] reported an increased prevalence of HCV infection in type-2 diabetic patients compared to the general population. However, none of the studies have demonstrated that the patients with type-2 diabetes have a greater risk of acquiring HCV infection, especially when they are dialysed in a unit with a high prevalence of HCV.

In a study from the Middle East, investigators observed a significantly higher HCV prevalence (57.4% *vs.* 35.2%, OR=2.462, 95% CI=1.338–4.542) and *de novo* HCV seroconversion rates (11.48% *vs.* 7.04%, OR=2.483, 95% CI=1.241–4.946) among type 2 diabetics, despite reasonably shorter dialytic age (time since commencement on HD) (32.6 *vs.* 50.6 months, OR=3.320, 95% CI=1.487–7.4810) as compared to nondiabetic patients undergoing HD. Researchers

concluded that acquiring HCV infection at a significantly shorter dialytic age was suggestive of greater vulnerability of ESRD patients with type-2 diabetes to HCV infection [12]. A combined effect of diabetes mellitus, uremia, oxidative stress, malnutrition impaired humoral and cell-mediated immunity could make ESRD patients susceptible to HCV infection [13, 14].

HCV infection is both a cause and a complication of chronic kidney disease (CKD). Extrahepatic manifestations are also vital and include mixed cryoglobulinemia, lymphoproliferative disorders, and HCV associated glomerulonephritis (GN). HCV infection also represents a major medical and epidemiological challenge in ESRD patients on RRT with dialysis or transplantation. In these settings, the presence of HCV correlates with higher rates of patient mortality. HCV-related complications after renal transplant include post-transplant diabetes mellitus, HCV-related GN, and chronic allograft nephropathy [15]. Additionally, HCV infection may lead to development of ESRD in a significant proportion of infected cases [16].

A large (n= 474,369, age: 18–70 years) retrospective nationwide study from the US investigating the association between HCV seropositivity, baseline CKD, and the development of ESRD during 3.5 years of follow-up reported that patients positive for anti-HCV antibody were more likely to develop ESRD, at a rate of 4.26 per 1000 person-years (95% CI=3.97–4.57) compared to 3.05 per 1000 person-years (95% CI=2.96–3.14) for HCV-seronegative patients. GN accounted for 6.2% of ESRD diagnoses in HCV-positive group *vs.* 2.8% in the HCV-negative group [16].

There is a paucity of data on the relationship between HCV infection and the development of type 2 diabetes mellitus among intravenous drug abusers (IVDAs) that form the single largest cohort with reported HCV prevalence as high as 60% to 90%, worldwide. Newly acquired IVDA-related HCV cases accounted for 68% of all HCV-infected patients between 1995 and 2000 in the US alone. The major difference between recently acquired case of HCV and those acquired before 1990's was the relative involvement of blood transfusion, a source

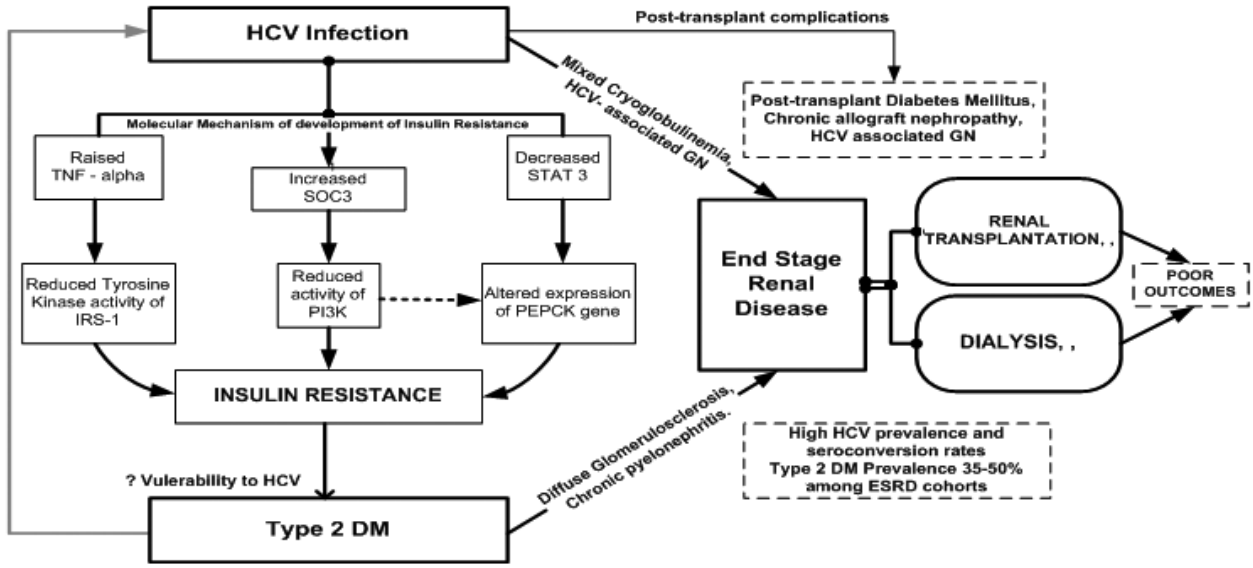

Figure 1. Schematic diagram of the proposed molecular mechanism of insulin resistance (IR) and hypothesis of type 2 diabetes mellitus and resultant end-stage renal disease following hepatitis C infection. Tumor necrosis factor α (TNF-α) is increased in the serum and liver of HCV-infected patients. TN90F induces IR by decreasing the tyrosin kinase activity of insulin receptor substrate 1 (IRS-1). High levels of suppressor of cytokine signalling 3 (SOC3) have been detected in association with IR in HCV infection. This effect was associated with reduced insulin-induced phosphorylation of the p85 subunit of phosphatidylinositol 3-kinase (PI3k) and SOC3. HCV can attenuate the activity of signal transducer and activator of transcription 3 (STAT-3). Glucose intolerance is associated with increased expression of the phosphoenolpyruvate carboxykinase (PEPCK) gene.

that is now extremely uncommon [17].

However, a cross-sectional study from New York involving drug abusers (n=557) who were recruited from a methadone treatment program found that HCV infection was strongly associated with diabetes mellitus (adjusted OR=2.9; 95% CI=1.3–6.4) after adjusting other confounding factors (age, race, unemployment, and body mass index). Nonetheless, the development of diabetes mellitus was in some way attributed to the use of antiretroviral medications for the treatment of the concomitant HIV infection [18]. Thus, regardless of remarkable resemblance in the routes of transmission of HCV infection among HD patients and IVDAs, we have only little evidence of the relationship between the latter group of patients and type 2 diabetes mellitus. [19] Is that not remarkable, as well?

The above-mentioned facts raise a few important questions:

What are the dynamics that prevent IVDAs from the development of type 2 diabetes mellitus in spite of incredibly high prevalence of HCV among them?

Should the current guidelines which recommend that "patients with ESRD and severe CKD must be screened for HCV," be also extended to include those with moderate CKD?

Should all the patients with HCV infection be routinely screened for CKD and glucose intolerance?

Could treatments effective in achieving sustained virological response alter the risk for development of type 2 diabetes and HCV-related renal disease?

Would the existing treatments used to delay the progression of CKD be also effective in subjects with chronic HCV infection?

Prospective studies, preferably cohort studies, should be conducted to answer these questions.

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